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HYPOTHYROIDISM IN CHILDHOOD.[1]

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THE clinical features of hypothyroidism are well known and are clearly set out in the textbooks. Nevertheless "More is missed by not looking than not knowing" remains a true saying—for example, one child in this series had an operation for umbilical hernia without the surgeon being aware she was a cretin; only later was this child referred by an infant welfare sister.

Some clinical features, not particularly emphasized in books, which can make the alert physician aware of the need for further investigation are short stature, immobility, pigment changes and anæmia.

Thyroid hormone stimulates growth, and in its absence the child is short and has delayed skeletal development. Moreover, the lower segment of the body, from the symphisis pubis to the ground, is particularly short, so that skeletal proportions remain infantile. The importance of linear measurements in infancy and childhood cannot be over-emphasized and they are often neglected.

The normal child is constantly on the move, and the lack of movement in a cretin is a valuable pointer to the diagnosis. Where a normal child is running round, or at least fidgeting, the cretin just sits.

[1]Read at a meeting of the Australian Pædiatric Association on April 23, 1961, at Canberra.

Icteric changes in the skin due to carotene are often found in the older cretin and these are well demonstrated in "Kodachrome" slides. With treatment the skin is restored to a normal colour. In the neonatal period persistence of jaundice may be the indicator for cretinism. The hair, which is usually brunette in the cretin, may become much fairer with treatment and in several children has become strikingly blonde.

Anæmia is almost always present in hypothyroidism, and may be the presenting symptom, though it is never an isolated phenomenon. It does not respond to iron therapy, but is relieved dramatically with thyroxine.

These and other symptoms and signs point to the need for fuller investigation, and here let us stress the dangers of the so-called therapeutic trial. In these days, when the accurate diagnosis of cretinism is always possible, there is no excuse for sloppy thinking which can and usually does lead to inadequate treatment if the diagnosis is correct, and to anxiety and worse in the patient and parents if it is not correct. Moreover, subsequent investigation to establish the diagnosis is likely to be delayed and will be confused by the taking of thyroid even in inadequate amounts.

The most useful screening test is radiological study of the epiphyseal development of the child. In hypothyroidism there will be delayed appearance of epiphyseal centres, so that the child's skeletal age is less than his chronological age. Epiphyseal dysgenesis, which is likely to become more marked in the early months of treatment, and changes such as notching of the lumbar vertebræ may

also be present. Other conditions, including hypopituitarism, may be associated with delayed epiphyseal development, and the only absolute evidence of hypothyroidism is the finding of a low serum protein-bound iodine level (the normal range in children is from 3·6 to 7·5 μg. per 100 ml.). This is technically a difficult test to perform, but in any case with even the slightest doubt it should be done. Other features, such as the serum cholesterol level, which is often raised though by no means always so, the hæmoglobin value, which is often low, and

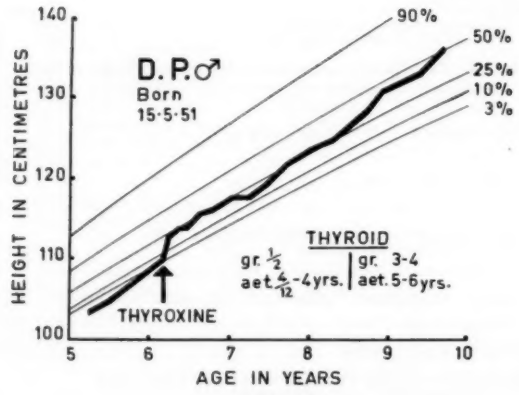

FIGURE I.

the serum alkaline phosphatase content, which is sometimes low, are not specific enough for diagnosis, though they may be of interest to the investigating physician.

Hypothyroidism has been divided by Wilkins (1957) into severe congenital (with definite symptoms within the first six months), mild congenital (with symptoms not readily evident prior to six months, but grossly manifest by six to 18 months) and acquired types (with the onset of symptoms occurring between two and 12 years).

In this series of 29 cases, 23 were severe, four were mild and in two the condition was acquired. Of the 29 patients, 20 were female and nine were male. Of the 20 females, 16 had the severe type, three the mild type and one the acquired type. Of the nine males, seven had the severe type, one the mild type and one the acquired type.

The age at diagnosis varied, but at least six cases were recognized before the age of three months and all these patients were inadequately treated.

Adequacy of treatment was assessed by the standards set by Smith, Blizzard and Wilkins (1957). These were as follows: (i) prompt and persistent disappearance of all clinical signs of hypothyroidism; (ii) restoration of normal rates of physical growth and osseous development; (iii) optimum dosage reached within three months of starting treatment. This time element is of special importance to stress, as in the time taken to achieve optimum levels of thyroid replacement therapy there is far too often unnecessary delay — quite apart from the inadequate dosage given.

There are minimal risks in giving too much, and great risks in giving too little.

In 12 out of 23 severe cases in this series treatment was inadequate for many months and often for years. There has not yet been sufficient time for follow-up to assess results of treatment fully, but so far the findings have confirmed the conclusions of Smith *et alii*—that is, early adequate therapy produces the best results in severe cretinism, but in mild cases late commencement of therapy may not result in mental impairment of as great degree as persists in some severe cretins even when adequately treated.

This interim report has been presented because certain facts disclosed that details of treatment were obviously wrong and needed correction. The series relates only to patients seen by me in Melbourne, but there is evidence to support the idea that the conclusions reached are valid for the whole of Australia.

Three illustrative case histories are presented.

CASE I.—The patient was a male, born on May 15, 1951 (Figure I), who was diagnosed as a cretin at the age of four months and treated with half a grain of thyroid daily for four years. The dosage was then increased gradually to three grains daily and for the next two years varied between two and four grains daily. When the boy was examined in June, 1957, aged six years and one month, he was still undersized and his skeletal age was that of a boy aged three and a half years, but whenever his dose of thyroid was increased he developed diarrhœa. The treatment was then changed to thyroxine (0·3 mg. daily) and the chart shows the progressive improvement in his height, with which was associated the

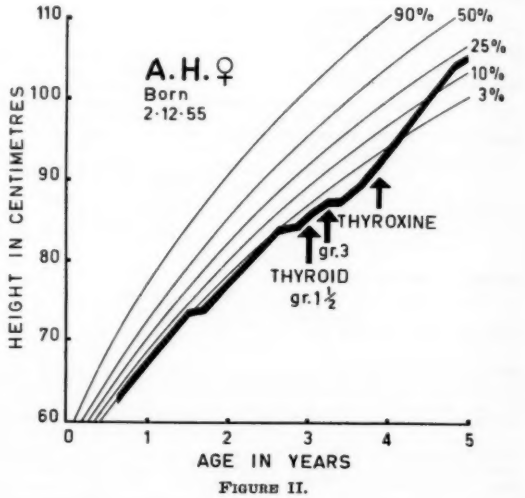

FIGURE II.

restoration to normal of his skeletal development and the cessation of diarrhœa. His appetite improved, his skin became clearer and he became more alert. He remains retarded educationally, but is attending a normal school quite satisfactorily.

CASE II.—The patient was a female, born on December 2, 1955 (Figure II), who was diagnosed as a cretin at the age of seven months and treated with one grain of thyroid daily till her second birthday, when the dosage was increased to one and a half grains daily. At the time of her third birthday her height was at the 3% level and her skeletal age was a little delayed; her serum cholesterol level was raised to 500 mg. per 100 ml. Three months later the thyroid dose was increased to three grains daily, but though there was some improvement clinically her height remained less than the 3% level and her skeletal age was reported as being only within the lower limit of normal. At this stage, just before her fourth birthday, thyroxine (0·3 mg. daily) was substituted for thyroid, with dramatic improvement. Not only did her height rapidly increase, but her epiphyseal development improved coincidently, she lost her sluggishness and became alert, her colour improved and all symptoms and signs of hypothyroidism disappeared. Her intelligence level was tested recently and found to be in the dull range of normal, but this also appeared to be improving.

CASE III.—The patient was a female, born on February 21, 1957 (Figure III), who was diagnosed as a cretin at the early age of three days. Treatment was then commenced with three-sixteenths of a grain of thyroid daily for three months, when it was increased to one grain daily and thereafter by stages to five grains daily by her third birthday. This should have been adequate therapy, but she still had the facial appearance and sluggishness of a hypothyroid individual, her height was less than the 3% level, her skeletal age was only 19 months, the serum cholesterol level was 278 mg. per 100 ml. and her serum protein-bound iodine level

was only 3·2 μg. per 100 ml. Treatment was therefore changed to thyroxine at the equivalent dosage of 0·5 mg. daily, but on this régime she developed toxic symptoms and has since been maintained on 0·3 mg. daily. The chart shows the steady increase in her height, and by February, 1961, her skeletal age was approaching normal, her serum cholesterol level was 122 mg. per 100 ml. and all clinical symptoms and signs of hypothyroidism had disappeared. Her intelligence level when tested in November, 1960, was found to be well up to her age level, apart from speech, which was somewhat delayed.

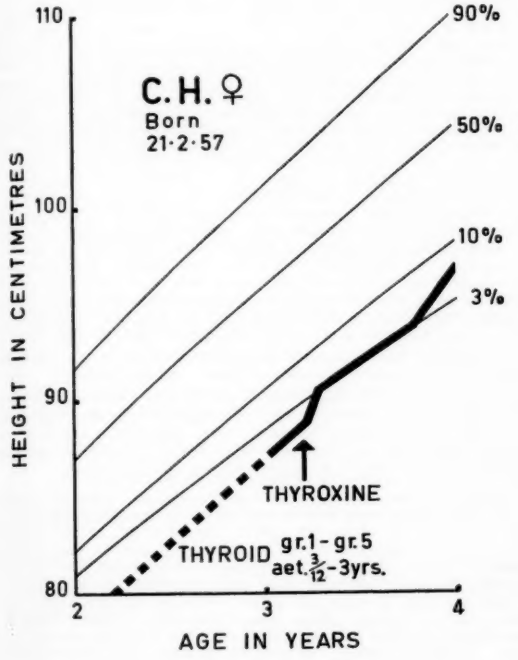

FIGURE III.

These three case histories were not isolated examples, but were typical of the other cases treated with thyroxine. *Thyroideum Siccum* B.P. has been for years the traditional therapy for hypothyroidism, but there is no doubt that it should now be considered outmoded.[1]

This premise has received strong support from Macgregor (1961) in an article which came to hand just before the presentation of this paper.

The equivalent dose of thyroxine 0·1 mg. is thyroid B.P. 60 mg. (one grain), but the latter is highly unreliable in its potency for a variety of reasons, well set out by Macgregor (1961), which do not need to be recapitulated here. In the treatment of cretinism a dosage schedule which has been found reasonable is as follows. First, thyroxine (0·025 mg.) should be given for two to three days; then 0·05 mg. up to two weeks; then 0·1 mg. for two weeks. At this stage one should increase the dose by 0·05 mg. at two-weekly intervals until 0·3 mg. is being given daily. It should be given at one time.

Summary.

1. Some clinical features of hypothyroidism have been described.

2. The need for accurate diagnosis before treatment is stressed. The serum protein-bound iodine level determination is the most important and valuable investigation. The use of a therapeutic trial of thyroid therapy is condemned.

3. A series of 29 cases of hypothyroidism is presented, and some results are analysed.

4. Treatment is often inadequate, and standards of adequate therapy have been outlined.

5. The use of thyroid B.P. is shown to be often ineffective. This drug should be replaced by thyroxine.

6. A dosage schedule for thyroxine is suggested.

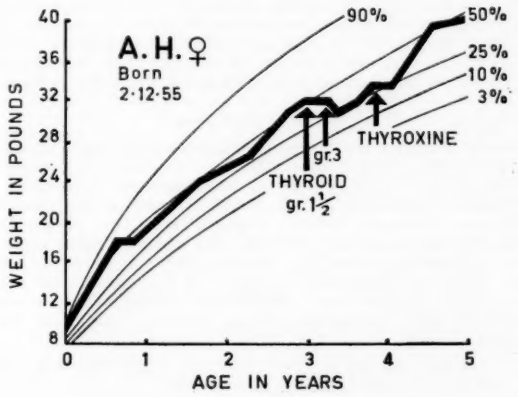

FIGURE IV.

Acknowledgements.

Grateful thanks are given to all those doctors, particularly my colleagues on the senior medical staff of the Royal Children's Hospital, who referred patients to me, and also to Mrs. D. Winikoff of the Diabetic and Metabolic Unit of the Alfred Hospital, who did all the determinations of the serum protein-bound iodine.

References.

MACGREGOR, A. G. (1961), "Why Does Anybody Use Thyroid B.P.?", *Lancet*, 1: 329.

SMITH, D. W., BLIZZARD, R. M., and WILKINS, L. (1957), "The Mental Prognosis in Hypothyroidism of Infancy and Childhood", *Pediatrics*, 19: 1011.

WILKINS, L. (1957), "The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence", Second Edition, Thomas: 88.

ACCIDENTAL DIGITALIS POISONING IN CHILDHOOD.[1]

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ACCIDENTAL digitalis[2] poisoning in childhood appears to be increasingly common. With an ever-aging population, digitalis is more frequently prescribed, and thus more opportunities exist for the drug to be obtained by children. Digoxin, the common preparation in use, is not unpleasant to the palate; if one tastes the tablet its vaguely sweet taste may be appreciated and one may readily understand how a child will ingest a large dose. Our early experience

[1] This premise has received strong support from Macgregor (1961) in an article which came to hand just before the presentation of this paper.

[1] Read at a meeting of the Australian Pædiatric Association, at Canberra on April 24, 1961.

[2] The word "digitalis" is frequently employed in this paper, according to common custom, to refer generally to the cardiac glycosides.

was limited to three mildly affected children. Treatment consisted of observation, with perhaps replacement of fluid and electrolyte losses due to vomiting.

In the past year five children suffering from severe accidental digitalis poisoning have presented at the Royal Alexandra Hospital for Children.

Having regarded this disease as a self-limiting one, we were shaken out of our complacency in 1960, when an apparently not very ill child died shortly after admission to hospital. Dr. J. Laing, Deputy Government Medical Officer for Sydney, has no record of any previous or subsequent deaths due to accidental digitalis poisoning (1961). This distressing death prompted the energetic management of children subsequently admitted for digitalis poisoning.

Clinical Features.

Table I shows the clinical features of the eight children in our series. Their ages (the 2 to 3 years age group predominating) were typical of the cases of poisoning in childhood examined at the Royal Alexandra Hospital for Children (Grigor, 1960). Digoxin was the preparation taken by seven of the children, and one took lanatoside C. The known ingested dose ranged from 2 to 6 mg., but the dose was unknown in three of the cases. We have encountered several cases of digitalis overdosage in children suffering from congenital heart disease, but these have been excluded.

Vomiting was the earliest and most prominent symptom. It usually occurred within a few hours, but was delayed for eight hours in the child who died and for 12 hours in the one who ingested lanatoside C. It recurred at frequent intervals and persisted until the child showed other evidence of recovery.

Oliguria was present in half the children and appeared to be related to the degree of vomiting. Drowsiness was present in all children to some extent, but, although it was an early feature, its degree did not always reflect the severity of the intoxication. Irregularities of the pulse were noted clinically, ranging from extrasystoles to pulsus bigeminus and marked sinus arrthythmia.

In three of the severely intoxicated children dilatation of the pupils was observed.

We cannot demonstrate any features which are more prominent in those severely affected, except to observe that the time from ingestion to vomiting appeared longest in the patient who died and the one who ingested lanatoside C. The severity of the poisoning did not appear to be related to the amount of digitalis which had been ingested. This is in keeping with experience of the therapeutic use of glycosides, in which dosage is judged by the clinical response.

Since the clinical features were so similar, we found the best guide to the severity of intoxication and the efficacy of treatment to be the electrocardiogram. Serum potassium level estimations were performed in the latter group of five cases, but were not found to be of value as a guide to treatment.

CASES I-III.—The three early cases in the series may be mentioned briefly. They were relatively mild cases and the electrocardiogram in one of this group, as seen in Figure I, shows *S-T* segment depression, as may be obtained with modest digitalis dosage. This electrocardiogram was taken two days after the patient's admission to hospital. However, a variety of arrhythmias is observed in digitalis poisoning and such may well have been found in this group had electrocardiograms been taken at an early stage.

CASE IV.—The fourth child in our series, a boy, aged three years, is alleged to have swallowed 5 mg. of his grandfather's digoxin tablets at 10.00 p.m. on January 25, 1960. His parents were not concerned, since he had fallen asleep and did not appear to be upset by the drug. He awoke at about 6.00 a.m. the next day and vomited a small amount of partially-digested food. Vomiting recurred frequently during the morning and he became drowsy. The local practitioner was not called until the afternoon, when the child was referred to the Royal Alexandra Hospital for Children 18 hours after ingesting the digoxin. At that time we considered the period of maximal toxicity to have passed. He was pale and drowsy, but easily roused. Although still vomiting, he did not appear desperately ill. His pupils were three-quarters dilated. However, he became more drowsy; his pulse rate, which was irregular, fell to 40 beats per minute and he died within an hour of admission. No electrocardiogram was taken in this instance. At autopsy, although the heart was slightly pale, no other obvious lesion was detected.

Children who presented subsequently with digitalis poisoning were treated more energetically. Gastric aspirations were performed and an electrocardiogram was taken on admission. Potassium chloride was given by the intravenous route. Our results may be best appreciated by considering the clinical histories of these children and the electrocardiographic changes.

CASE V.—The patient was a girl, aged one year 11 months, who was discovered eating her grandfather's digoxin tablets at 2.00 p.m. on June 18, 1960; the amount taken was not known. One hour later, she vomited her lunch, and she continued to vomit small amounts of brown-stained material during the day. By nightfall she was pale, drowsy and still vomiting, but it was not until 3.00 a.m. on June 19, 1960—that is, 13 hours after ingesting the tablets, that she presented at the casualty department. On examination she was a pale, drowsy, ill-looking infant with widely-dilated pupils. Her pulse rate was 96 beats per minute and there were frequent extrasystoles; the blood pressure was 110/70 mm. of mercury and she was mildly dehydrated. Gastric aspiration produced a poor result. The vomiting continued and she became stuporose. Her pulse rate, which was irregular, fell to 60 beats per minute and the blood pressure dropped to 70/40 mm. of mercury. The electrocardiogram revealed a Wenckebach phenomenon and shortly afterwards a bundle branch block, with atrio-ventricular dissociation (Figure II). Despite the fact that no urine had been passed since the ingestion of the tablets, intravenous administration of potassium chloride in a 5% dextrose solution was commenced at 4.15 a.m. Tracings at 4.33 a.m. showed first-

TABLE I.

Summary of Clinical Details of Cases of Digitalis Poisoning.

Case Number.	Age.	Sex.	Drug and Approximate Dose.	Interval between Ingestion and Vomiting. (Hours.)	Symptoms.			Signs.		Result.
					Vomiting.	Drowsiness.	Other.	Pulse.	Urinary Output.	
I	2 years	M.	Digoxin, 2 mg.	3·5	+++	++	Dehydration +	Regular	Satisfactory	Recovery
II	2 years 3 months	F.	Digoxin, unknown amount	1·0	+++	+	0	Irregular	Satisfactory	Recovery
III	4 years 9 months	F.	Digoxin, 4–5 mg.	0·75	++++	0	0	Irregular	Poor	Recovery
IV	2 years 1 month	M.	Digoxin, 5 mg.	8·0	+++	++	Pupil dilatation	Irregular	?	Death
V	1 year 11 months	F.	Digoxin, unknown amount	1·0	+++	++	Pupil dilatation	Irregular	Poor	Recovery
VI	2 years	M.	Digoxin, unknown amount	3·0	++	+	Pupil dilatation	Irregular	Satisfactory	Recovery
VII	3 years	M.	Digoxin, more than 6 mg.	0·5	+	Slight only	0	Irregular	Poor	Recovery
VIII	5 years	M.	Cedilanid, ? 10 mg.	12·0	++	Sleep	Abdominal pain	Irregular	Satisfactory	Recovery

degree heart block with a period of ventricuar tachycardia, and one at 5.51 a.m. first-degree heart block, with a few sinus beats initiating atrio-ventricular conduction defects of the Wolff-Parkinson-White type. Vomiting ceased at 6.15 a.m., after 20 mEq of potassium as potassium chloride had been given, and she cried for the first time since admission; the electrocardiogram revealed first-degree heart block and digitalis effect. The blood pressure was 100/60 mm. of mercury. The improvement was maintained and subsequent tracings showed a shortening of the *P-R* interval. By 8.15 a.m., after having had 30 mEq of potassium chloride in 300 ml. of a 5% dextrose solution over a four-hour period, she was alert and appeared well; early peaking of the *T* wave was seen

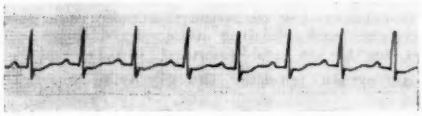

FIGURE I.

ST segment depression in the electrocardiogram of a normal girl, aged five years, who had swallowed digoxin tablets. Such changes are observed in ordinary digitalis therapy.

on the electrocardiogram and the potassium chloride administration was suspended (Figure III). Her progress was excellent. By the afternoon she was taking fluids orally quite well and passing urine. Her pulse was regular, and later in the day the electrocardiogram returned to normal.

This patient illustrates severe digitalis intoxication, with dramatic improvement following intravenously administered potassium chloride. It is noted that potassium was administered in the presence of doubtful renal function, but this risk was considered less than that of allowing her to continue untreated. Early evidence of hyperkalæmia was detected on the electrocardiogram, but the potassium chloride infusion produced no other untoward effect.

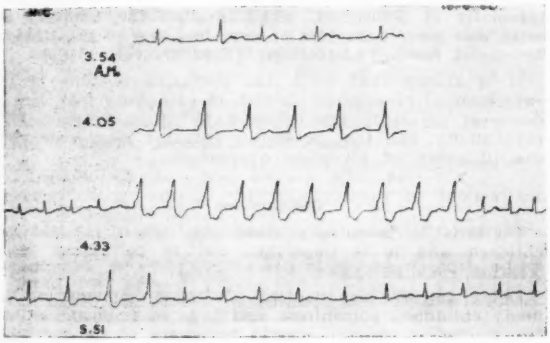

FIGURE II.

Various changes observed in the electrocardiogram of a girl, aged two years, who had accidentally ingested digoxin tablets. The upper tracing shows the Wenckebach phenomenon. The second tracing reveals atrioventricular dissociation and bundle branch block. The third tracing shows sinus beats with first-degree heart block, before and after a short period of ventricular tachycardia. In the early portion of the lower tracing there are three complexes of the Wolff-Parkinson-White type.

CASE VI.—A boy, aged 2 years, ingested an unknown quantity of digoxin tablets at 12.30 p.m. on October 6, 1960; the tablets had belonged to his grandmother, who had died one year previously. Vomiting commenced after three hours and he was taken to a district hospital, where gastric lavage was performed, and at 6.30 p.m. he was referred to the Royal Alexandra Hospital for Children. On examination he was pale and drowsy and had an irregular pulse, with a rate of 60 to 70 beats per minute. An electrocardiogram showed a Wenckebach phenomenon and 2:1 atrioventricular block. At 7 p.m., after several periods of vomiting, intravenous potassium chloride administration (in a 5% dextrose solution) was commenced. One and a half hours later he passed urine for the first time since ingestion of the digitalis. Twenty milliequivalents of potassium chloride had been administered by 9.00 p.m., at which time vomiting ceased and he was much brighter. The electrocardiogram at this time showed a marked first-degree heart block. By 12 o'clock midnight he appeared well. However, his pulse remained irregular and both first-degree block and 2:1 atrioventricular block were present on the electrocardiogram; 40 mEq of potassium chloride had been given over a five-hour period. His improvement was maintained, and by 3.00 a.m. his pulse was regular and only first-degree heart block was seen on the electrocardiogram. The potassium chloride administration was suspended at this juncture, a total of 50 mEq of potassium having been given. The first-degree heart block became less marked and by 10.00 a.m. the electrocardiogram was normal.

CASE VII.—A boy, aged three years, ingested at least 6 mg. of his grandmother's digoxin tablets at 1.00 p.m. on November 6, 1960. He commenced to vomit three hours later and the family practitioner performed gastric lavage and gave him an injection of nikethamide. The vomiting continued, occurring once every half hour, and he became increasingly drowsy. He was referred to the Royal Alexandra Hospital for Children at 7.30 p.m.; there examination revealed a

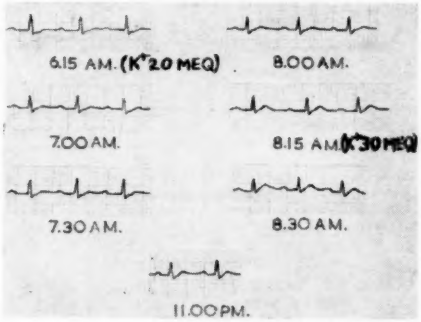

FIGURE III.

The electrocardiogram of the same patient as in Figure II after treatment with intravenously-administered potassium chloride. Peaking of the *T* wave is observed in the 8.15 a.m. and 8.30 a.m. tracings, especially when compared with the 7. a.m. and 7.30 a.m. tracings.

pale, drowsy, ill infant. His pulse was irregular and the electrocardiogram showed nodal rhythm (Figure IV). Urine had not been passed since ingestion of the digitalis. Intravenous administration of potassium chloride in a 5% dextrose solution was commenced at 9.00 p.m., and, after 10 mEq had been given in one hour, he was restless and still vomiting. The electrocardiogram showed a first-degree heart block and a 2:1 atrioventricular heart block. By 12 o'clock midnight, after 25 mEq of potassium chloride had been given, the electrocardiogram showed a sinus arrhythmia, but there was little change in the patient's condition. He passed urine at 2.30 a.m., after 35 mEq of potassium had been given, but the vomiting continued. Nodal brachycardia was seen on the electrocardiographic tracing. His condition improved rapidly over the next few hours and vomiting ceased later in the morning. By 12.30 p.m., having received 75 mEq of potassium chloride in a litre of 5% dextrose solution, he was bright and taking fluids by mouth very well. The potassium infusion was stopped and he remained well. Marked sinus arrhythmia persisted for a day before the electrocardiogram returned to normal.

CASE VIII.—A boy, aged 5 years, ingested an unknown amount of his mother's lanatoside C at about 9.00 p.m. on February 2, 1961. The family practitioner was contacted by telephone and he reassured the parents that the tablets were harmless. Vomiting did not commence until 9.00 a.m. on February 3, and occurred at frequent intervals during the day. The family doctor was called again, and he prescribed barley sugar, salt and laxative. However, the vomiting continued throughout the night, and by the following morning (February 4) the boy had become drowsy and was referred to the Royal Alexandra Hospital for Children. On examination, he was mildly dehydrated and drowsy. His pulse rate was 70 beats per minute and sinus arrhythmia was present. The electrocardiogram showed marked sinus

arrhythmia and the usual effect of digitalis on the *ST* segment. Intravenous therapy was commenced, 45 mEq of potassium chloride being given over 24 hours. The vomiting soon ceased and he made a rapid recovery. However, the well-marked sinus arrhythmia persisted for two days. This was probably the mildest of the recent cases, but it presents several important features. Of particular note is the twelve-hour delay before the occurrence of vomiting. Delay in treatment did not influence the outcome, but experience with other cases shows that serious consequences may thus ensue.

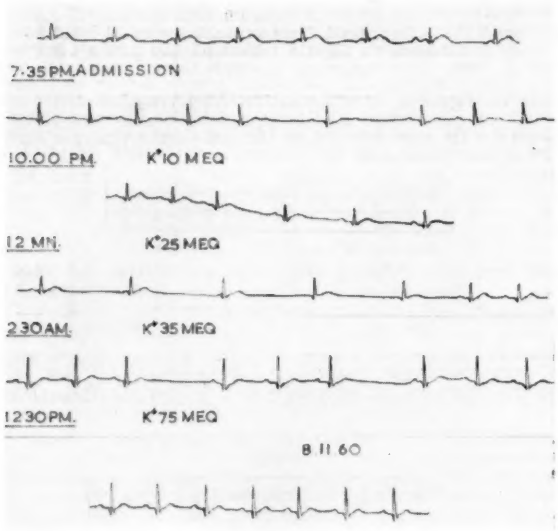

FIGURE IV.

Electrocardiograms from a boy, aged three years, who had accidentally taken digoxin tablets. The tracing taken at 7.35 p.m., on his admission to hospital, shows a nodal rhythm. The 10 p.m. tracing reveals first-degree heart block and 2 : 1 atrioventricular block; in the tracing taken at 12 midnight sinus arrhythmia appears. By 2.30 a.m. nodal bradycardia is present. The tracing at 12.30 p.m. shows sinus arrhythmia and the tracing taken the next day is normal.

Recommendations for Management of a Child with Digitalis Intoxication.

Emptying the Stomach.

Emptying of the stomach contents should be performed as soon as possible, even if digitalis has been ingested many hours earlier or vomiting has occurred. This is achieved either by gastric aspiration followed by lavage, or by induced emesis, which may be more efficient, as shown in experimental animals (Arnold *et alii*, 1959). Tincture of ipecacuanha is recommended to induce emesis.

Intravenous Potassium Chloride Administration.

Treatment with potassium chloride has been recommended by Lown *et alii* (1954), Robinson (1960), Sapin (1960), and Shrager (1957). Five to 20 mEq of potassium per hour is an approximate range of dose. This is given as a solution of potassium chloride (80 mEq of potassium per litre of 5% dextrose solution). It is difficult to be dogmatic about dosage, since this is influenced by the electrocardiographic findings, the potassium infusion being suspended when the electrocardiogram approaches normal, or when peaking of the *T* wave occurs. Large doses of potassium in the presence of oliguria must be given carefully, and if signs of digitalis intoxication are persistent and more potassium is required, very careful observation of the electrocardiogram is necessary. If hyperkalæmia occurs, it is detected early by the electrocardiogram and the potassium administration is suspended. Oral administration of potassium salts is contraindicated because of vomiting.

Electrocardiogram.

Constant electrocardiographic control has been referred to above. Other forms of treatment, such as chelating agents and procaine amide, were not employed.

Pharmacology.

The theories of the mode of action of cardiac glycosides and their relationship to cation concentration, particularly of potassium and calcium ions, have been admirably reviewed by Hajdu and Leonard (1959).

It is uncertain whether the glycoside exerts its chief effect on the muscle membrane, thus rendering it more permeable to potassium ions which move out of the cell during depolarization, or whether it actually influences the potassium-binding properties of the contractile protein elements. Actin and myosin, when united, contract with the help of the high-energy phosphate bond from ATP (adenosine triphosphate). Calcium ions are not directly related to the effect of glycosides, but in their presence the glycosides are more effective. However, it is potassium which concerns us chiefly in therapy, because experimentally it is the ion which appears to be more directly related to the effect of digitalis on the heart muscle cells.

The defect in the failing heart is probably in utilization of the energy which is derived from metabolic sources (ATP and creatine phosphate). It is upon energy utilization that glycosides exert their effect in the failing heart, but if the effect of glycoside upon actin, myosin and ATP is too great, actin and myosin will have difficulty in parting and contractures and arrhythmias will develop in the muscle. It is the intracellular ionic concentration, especially of potassium, which decides the tendency of actin and myosin to part or combine, and so the tension developed during contraction (Szent-Gyorgi, 1952).

It is known that when the perfusing medium of an experimental preparation is rich in potassium ions, larger doses of glycoside are required to affect heart muscle rhythmicity, and that potassium infusion may counteract the ill effect of glycoside overdosage.

Conclusions.

Digitalis is potentially dangerous when ingested by children and it is important not to be casual when treating such patients.

Delay in seeking medical advice is common, as in many childhood poisonings, and it is of importance that the medical profession should be aware of the potential dangers of digitalis poisoning, even though the child may not appear ill. Some of the children were examined initially by the family practitioner, who reassured the parent and prescribed placebo treatment only, with the result that by the time the children were eventually admitted to hospital, they were very ill.

Most of the children obtained the digitalis from a grandparent, where no measures were taken to prevent easy access to the drug. This fact emphasizes that such dangerous drugs should be placed out of reach of the child's inquisitive hands. Perhaps the bottle should be labelled, so that at least adults may be aware of its danger to children.

Of the clinical features, vomiting and drowsiness are early symptoms, although they may be delayed, even in the severely affected child. Dilatation of the pupils is an interesting feature, which seems to occur in the severely intoxicated child but is not referred to in the excellent description of the symptomatology by Goodman and Gilman (1955).

A variety of arrhythmias is observed on the electrocardiograms, and these are the best index to the severity

of the intoxication. Sinus arrhythmia appears to be more evident in those intoxicated with digitalis than in normal children.

Early emptying of the stomach combined with intravenous potassium chloride administration under constant electrocardiographic control appears the most satisfactory form of therapy.

It is appropriate to conclude by emphasizing once more that digitalis intoxication in childhood is potentially lethal, but with energetic treatment the outlook is good.

Summary.

Accidental digitalis intoxication in childhood is a serious disease, which appears to be increasingly common.

Five severely affected children presented in the past year. The first of these died, but the remaining four were successfully treated with potassium chloride given intravenously; their histories are presented.

Vomiting and drowsiness are the early symptoms, although vomiting may be delayed, with possible serious consequences to the child.

The electrocardiogram is the best method of assessing the severity of the intoxication.

Early emptying of the stomach and administration of potassium chloride intravenously, under constant electrocardiographic control, appear to be a satisfactory method of treatment.

The pharmacology of digitalis and the rationale of potassium treatment are discussed.

The awareness of the potential dangers of accidental digitalis poisoning is stressed and early admission to hospital is advised.

References.

ARNOLD, F. J. *et alii* (1959), "Evolution of the Efficacy of Lavage and Induced Emesis in Treatment of Salicylate Poisoning", *Pediatrics*, 23: 286.

GOODMAN, L. S., and GILMAN, A. (1956), "Pharmacological Basis of Therapeutics", Macmillan, New York: 668.

GRIGOR, W. G. (1960), "Accidental Ingestion of Poison in Childhood", MED. J. AUST., 2: 175.

HADJU, S., and LEONARD, E. (1959), "The Cellular Basis of Cardiac Glycoside Action", *Pharmacol. Rev.*, 2: 173.

LAING, J. (1961), personal communication.

LOWN, B., and LEVINE, S. A. (1954), "Current Concepts in Digitalis Therapy", *New Engl. J. Med.*, 250: 771.

ROBINSON, S. J. (1960), "Digitalis Therapy in Infants and Children", *J. Pediat.*, 56: 536.

SAPIN, S. O. (1960), "Digitalis Therapy in Pediatrics", *Quart. Rev. Pediat.*, 15: 41.

SHRAGER, M. W. (1957), "Digitalis Intoxication", *Arch. intern. Med.*, 100: 881

SZENT-GYORGYI, A. (1952), "Contraction in Heart Muscle Fibre", *Bull N. Y. Acad. Med.*, 28: 3.

DEFECTS OF THE ATRIAL SEPTUM.[1]

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IN February, 1960, a cardiac surgery unit was established at the Royal Children's Hospital, Melbourne. In its first 15 months (up to early April, 1961) this unit has treated 50 patients with one or more defects in the atrial septum. This paper is an account of experience gained with those 50 patients.

Embryology.

Essentially the heart is formed during the first six weeks of fœtal life. At first the heart is a simple tube which can be differentiated into several chambers; both caval and pulmonary venous blood drains into the sinus venosus, from whence it passes to a single atrium, a single ventricle, the bulbus cordis and the truncus arteriosus. During the fourth, fifth and sixth weeks of fœtal life, this series of chambers becomes divided into right and left halves by the development of septa and heart valves (Figure I). Some of the chambers disappear, leaving two atria and two ventricles. Incomplete development or fusion of septa, or improper involution of those chambers which usually disappear, results in congenital cardiac defects, the commonest group of which is found in connexion with the atrial septum.

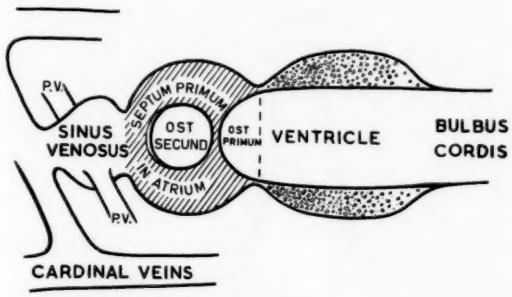

FIGURE I.

Scheme to show early heart development. Note that the vena caval and pulmonary venous blood drains into sinus venosus. The ostium primum and the ostium secundum are indicated in the developing atrial septum.

As the atrial septum grows towards the region of the ventricles from the sinus venosus, a hole is gradually filled in by growing tissue (Figure I). This hole is known as the ostium primum, and it is obliterated by fusion of the caudal end of the atrial septum with endocardial cushions which have been forming a large part of the ventricular septum and of the atrioventricular valves. Failure of fusion of this end of the atrial septum with the ventricular septum results in an atrial septal defect commonly known as the ostium primum type of atrial septal defect. However, as such a defect is commonly associated with abnormality of the ventricular septum and of the atrioventricular valves, it is better to call such a defect a persistent common atrioventricular canal, either partial or complete. The hole connecting the single atrium to the single ventricle in the very earliest stage of heart development is known as the atrioventricular canal. When this canal is incompletely divided into atrioventricular valves, it is reasonable to refer to the resulting abnormality as a persistence of the early canal (Figure II).

While the ostium primum at the ventricular end of the atrial septum is obliterating, a second hole forms in the middle region of the atrial septum—the ostium secundum (Figure I). During the next two or three weeks the ostium secundum is filled in almost completely, except for a small slit remaining as the foramen ovale. The latter foramen is essential for fœtal circulation, but is usually obliterated during the first few weeks after birth. Should the ostium secundum fail to be almost completely obliterated a large atrial septal defect develops. In many instances atrial septal tissue in the region of the ostium secundum is absent, resulting in an atrial septal defect much larger than if the ostium secundum persisted alone. All defects of the atrial septum involving the region of the ostium secundum, whether they extend beyond this region or not, are known as the ostium secundum type of atrial septal defect. In this unit it is preferred to refer to all such atrial septal defects as of the foramen ovale type (Figure III).

(In this extremely over-simplified brief account, for purposes of clarity, no reference has been made to the development of the septum primum and the septum secundum in the atrial region.)

[1] Read at a meeting of the Australian Pædiatric Association on April 21, 1961, at Canberra.

At the cephalic end of the atrium the septum fuses with the atrial wall at a time when the sinus venosus is almost completely disappearing. Normally, the only remnant of the sinus venosus in the adult heart is found in a region of the left atrium between the pulmonary veins. Should such involution be incomplete, part of the sinus venosus persists as a small chamber, into which drains the superior vena cava and the right pulmonary veins (wholly or in part). Almost always the atrial septum fails to fuse with the sinus venosus tissue, resulting in a high atrial septal defect. In the post-natal heart this abnormality gives the appearance of a high atrial septal defect with some or all of the right pulmonary

FIGURE II.

Persistent atrioventricular canal, showing an ostium primum defect in the atrial septum and clefts in the septal cusps of the atrioventricular valves. Through the cleft is shown a free margin of the ventricular septum, indicating a defect in the latter.

veins draining into the lower end of the superior vena cava. This combination is known as the sinus venosus type of atrial septal defect (Figure IV).

Types of Atrial Septal Defect.

On an embryological basis defects in the atrial septum may be classified into three main groups.

The first of these is the sinus venosus type, which is due to partial persistence of the sinus venosus. (Note that if the sinus venosus completely persists the result is one form of total anomalous pulmonary venous connexion. This is to be enlarged upon in another paper.) (Figure IV.)

The second is the foramen ovale type, most commonly known as the ostium secundum type, which is due to persistence of the ostium secundum with or without absent atrial septal tissue in the vicinity (Figure III).

The third is the persistent common atrioventricular canal. The atrial septal element of this defect is often known as the ostium primum type of atrial septal defect. (It is often referred to as the atrioventricular canal or the atrioventricularis communis.) (Figure II.)

Diagnosis.

Most cases have been uncomplicated and symptomless, and have been diagnosed during a routine examination for some non-cardiac lesion. Clinical signs of such atrial septal defects are often minimal, consisting of a soft ejection murmur over the outflow tract from the right ventricle and fixed wide splitting of the pumonary second

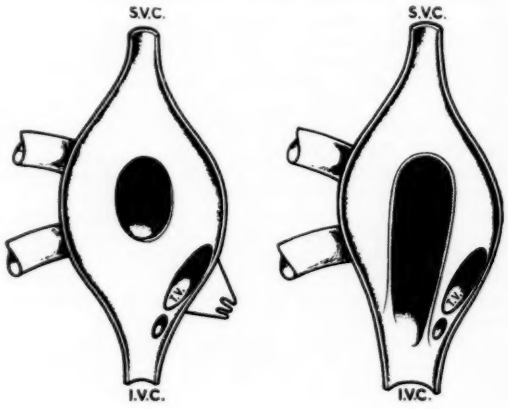

FIGURE III.

Two types of foramen ovale (ostium secundum) defect in the atrial septum.

sound—that is, the aortic and pulmonary valve closures are heard separately at all times, not coming together on expiration as occurs in the normal child. Radiographic examination confirms the suspected diagnosis by showing enlargement of the right atrium, the right ventricle and the pulmonary vascular tree. The electrocardiograph shows evidence of hypertrophy of the right atrium and the right ventricle, with a right bundle branch block pattern as well as right axis deviation. In such cases sometimes the sinus venosus type may be differentiated from the foramen ovale type of atrial septal defect by radiological appearances, in that the anomalous drainage of the right lung into the superior vena cava can occasionally be seen on a plain X-ray film. However, in this unit, this radiological sign has been found to be most unreliable. On the other hand, cardiac catheterization has always enabled one to differentiate between the sinus venosus and the foramen ovale types by showing in the former the high oxygen content in superior vena caval blood and by the passage of the cardiac catheter out into the anomalous veins from the superior vena cava.

A persistent common atrioventricular canal in its complete form is diagnosed by signs of a ventricular septal defect and the finding of a high oxygen saturation in the right atrial blood on cardiac catheterization. This is not a common form fortunately. Much more commonly, atrioventricular canals occur as ostium primum atrial septal defects with a split mitral valve and the latter quite often causes a mitral systolic murmur. In some cases the systolic murmur heard at the apex of the heart is not obviously different from that heard in the pulmonary area and a phonocardiogram has been helpful in deciding this point. Many cases of partial persistent common atrioventricular canal are not associated with any mitral incompetence at all and in these clinical and radiological signs are exactly the same as those of the foramen ovale and the sinus venosus types of atrial septal defect.

However, the electrocardiogram is very reliable in the differentiation of these partial atrioventricular canals, in that it almost always shows left axis deviation in contrast to the right axis deviation of other forms of atrial septal defect.

In this unit much importance is attached to the electrocardiogram in cases of atrial septal defect, in an attempt to select all cases of atrioventricular canal from the foramen ovale and the sinus venosus types. Patients with the former lesion undergo surgery with the aid of a heart-lung by-pass, while in the rest the operation is performed through the atrial well. In practice it means that patients

FIGURE IV.
Sinus venosus type of defect. A high defect in the atrial septum combined with drainage of veins from the right lung into the superior vena cava.

whose electrocardiograms show left axis deviation are connected to the heart-lung machine and those having right axis deviation are sewn onto an atrial well. The electrocardiogram has been misleading in four instances; one patient with the ostium primum type of atrial septal defect (with no abnormality of the atrioventricular valve and without ventricular septal defect) had right axis deviation and was repaired through an atrial well, while three patients with the foramen ovale type of atrial septal defect had left axis deviation and were repaired with the aid of heart-lung by-pass.

Treatment.

Preoperative Preparation.

The patient is admitted to the surgical ward two or three days before operation, to become acquainted with members of the cardiac surgical unit and for investigations such as radiological examination, electrocardiography, blood typing and cross matching. Two bottles of blood are set aside for patients who are to be operated upon through the atrial well and six to 10 bottles (depending on the patient's weight) of freshly-drawn heparinized blood are prepared for those who are to be operated upon with the aid of heart-lung by-pass. Digitalis is reserved for patients in cardiac failure and therefore is rarely used.

A skin test is made for penicillin sensitivity, for in all patients found in this way to be insensitive to the drug large doses of penicillin are given intravenously during the operation. Ten million units per 70 kg. of body weight are given for each hour of general anæsthesia. This loads the tissues with penicillin, so that any penicillin-resistant staphylococci falling into the tissues during operation will be destroyed by penicillin before the bacteria produce penicillinase, which is the cause of their resistance to the drug (Nancy Hayward, personal communication). Before this penicillin régime was used, one or two cases of minor wound infection due to penicillin-resistant staphylococci occurred, but since penicillin has been used

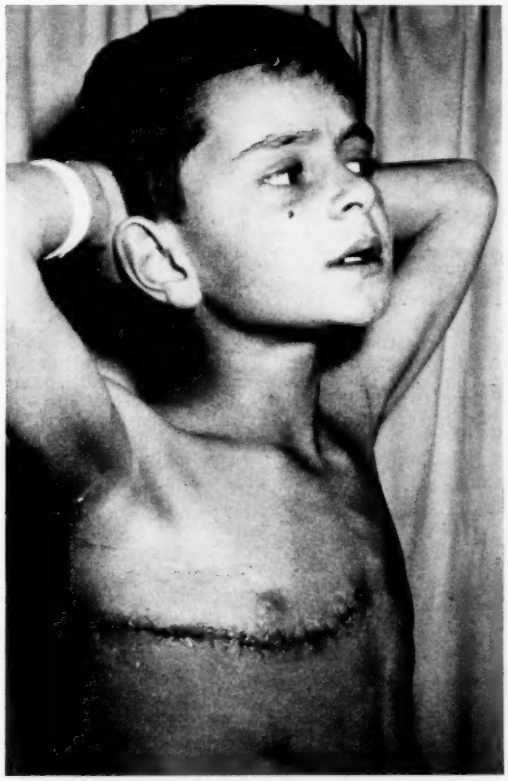

FIGURE V.
Repair of atrial defect through the atrial well. Extent of anterolateral thoracotomy.

during operation no staphylococcal infection has occurred at all. There have been no reactions to penicillin observed in this series.

Operation.

All patients considered not to have atrioventricular canals are operated upon through the atrial well in the following manner. Through a right anterior thoracotomy incision underneath the fourth rib (Figure V), the pericardium is exposed and opened by a semilunar incision convex forwards with its two ends based on the superior vena cava and the inferior vena cava. The resulting flap of pericardium is most useful in the retraction of the right lung from the region of the right atrium. Through the intact right atrial wall the septum is palpated, and usually the presence of a foramen ovale or sinus venosus type of atrial septal defect is confirmed. Of course, in the sinus venosus type, the veins from the right lung are seen entering the superior vena cava. Part of the right atrial wall from the tip of its appendage down to the

inferior vena caval orifice is excluded from the rest of right atrium by the application of a Donald clamp. An atriotomy is made in this excluded portion and to the cut edges of the atriotomy is anastomosed the lower end of a "Latex" atrial well (Figure VII). Originally atrial wells were imported from America (made by Davol Company), but more recently very satisfactory wells have

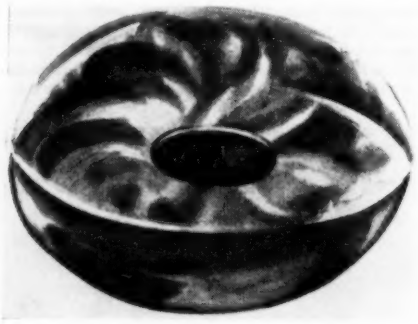

FIGURE VI.
Through a glass cone the intracardiac structures and the steps of the operation may be seen.

been made in Melbourne at much lower cost by the Ansell Rubber Glove Company. Heparin, in a dosage of 3 mg. per kilogram of body weight, is administered to the patient and the Donald clamp is removed. In most cases blood rises in the atrial well to a height of 4 to 6 cm. In some cases, when pulmonary hypertension or cardiac failure is present (when the right atrial pressure is much higher), blood rises to a correspondingly higher level in

FIGURE VII.
Photograph of the margin of a foramen ovale defect shown through a glass cone.

the well. A series of conical glass instruments has been made for the inspection of intracardiac structures and with these atrial septal defects can be inspected, as can mitral and tricuspid valve action, as well as caval and often pulmonary venous orifices (Figures XI and XII). In some cases the atrial septal defect is repaired by a few mattress sutures, but in most a patch of "Ivalon" sponge is sewn into the defect (Figures VI to X). Whether there are pulmonary veins draining into the right atrium or into the superior vena cava, and whether the atrial septal defect is of the foramen ovale or the sinus venosus type, is unimportant. All these atrial septal defects are readily repaired through an atrial well. Each stage of the repair can be checked by inspection with the glass cone, but mostly the whole procedure is done by palpation alone. The atrial well is removed, the atriotomy is sewn up and "Polybrene" (4·5 mg. per kilogram of body weight) is administered, to neutralize the effect of heparin. A drain tube is placed in the right side of the chest and the latter is closed. Measured blood loss (usually 200 to 300 ml.) is replaced. Rarely has one of these patients required more than 1 unit of blood during his whole

FIGURE VIII.
Step I in the repair.

stay in hospital. As a rule these patients waken quickly on their way back to the ward, usually two to two and a half hours after leaving it. They often eat a light tea on the day of operation, sit out of bed next day and go home on the tenth day.

Patients diagnosed as having an atrioventricular canal, partial or complete, are operated on with the aid of heart-lung by-pass as follows. The heart is exposed by a bilateral anterior thoracotomy underneath each fourth rib and its cartilage, with transverse section of the sternum. The superior vena cava and an internal mammary artery are cannulated and connected to an electromanometer for continuous pressure measurement. In many cases arterial blood from the heart-lung machine is pumped back into the patient's aorta by the femoral artery, exposed from the thigh, or into the ascending arch of the aorta by the anastomosis of a tube to this vessel. However, recently the external iliac artery has been used for this purpose, and has been exposd by a muscle-splitting incision in the right iliac fossa. Slings are placed around the venæ cavæ, a catheter is placed in the left atrium and the heart-lung machine, primed with the necessary volume of freshly-drawn, heparinized blood, is brought up to the table. This machine is of the Kay-Cross rotating-disc type (Figure XIV). Its pump is of the occluding-roller pattern. The whole machine has been constructed by the Pemco Company, Cleveland, Ohio, and it is found to be eminently satisfactory, being very simple indeed to use. Lately a water-jacket heat exchanger

has been used in the circuit to maintain the blood and the patient at normal temperatures instead of the electrical heating coil wrapped around the oxygenator. The heat exchanger has been very satisfactorily used in this way. It has not been used to cool any patient with an atrioventricular canal below normal temperatures, and such cooling is considered to be completely unnecessary.

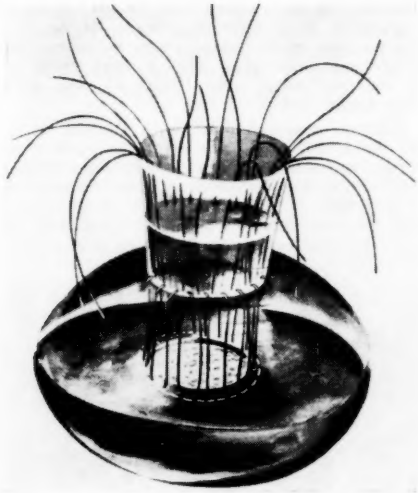

Figure IX.
Step II in the repair.

Cannulæ are placed through the right atrial wall into the superior vena cava and the inferior vena cava, and these are connected to the venous drain tube leading to the heart-lung machine. When all is ready, the heart-lung machine is turned on as blood is allowed to syphon out of the venæ cavæ into the machine. Slings around

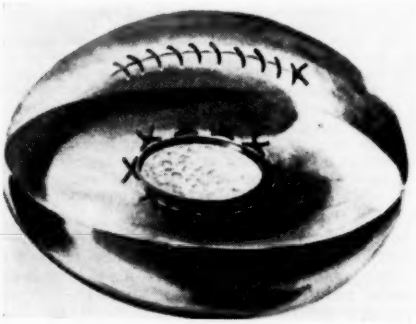

Figure X.
Step III in the repair.

the venæ cavæ and the contained cannulæ are tightened, so that all the caval blood must now flow into the machine. The left atrial cannula is connected to a source of suction and this is now turned on so that all blood coming from the lungs into the left atrium is sucked away into the machine. Before the right atrium is opened and the congenital defect is inspected a catheter is fixed into the left ventricle via its apex and this catheter is connected to the heart-lung machine. Its purpose is to allow air tending to collect in the left side of the heart to escape freely from the latter, rather than be pumped by the left ventricle into the aorta. The right atrium is then opened and the defect can be seen. In most cases a split is found in the anterior commissure of the mitral valve, and this is repaired by direct sutures before the ostium primum defect in the atrial septum is repaired with a patch of finely-woven "Teflon" material. In some cases a split in the tricuspid valve is now repaired, but it most cases this is not necessary. In one case there was an associated ventricular septal defect underneath the split valves and this ventricular septal defect was repaired by sewing the upper margin of the ventricular septum to the patch in the atrial septum, passing stitches through the valve cusps. When the cardiac septa are seen to be intact, left atrial suction is ceased and bronchial blood is allowed to fill the left side of the heart, expelling air

Figure XI.
Step IV in the repair.

through the left ventricular vent. If bronchial blood is insufficient for this purpose, a dextrose-saline solution is allowed to flow into the left atrium via its catheter. While this is being done, the right atriotomy is repaired, air being expelled from the right side of the heart as the latter fills up with coronary sinus blood. Cannulæ in the left atrium and the left ventricle are removed and the patient is gradually made independent of the heart-lung by-pass. In all cases the heart has picked up rapidly and well and cannulæ have been quickly removed from the venæ cavæ. When a normal blood volume has been restored, as shown by arterial and venous blood-pressure measurements, the arterial cannula is removed and the artery repaired. A drainage tube is placed in each side of the chest and the latter is closed. These patients go back to the ward, are soon awake, usually sit out of bed on the second day and go home about 14 to 20 days after operation.

Results.

Fifty-three defects have been closed in 50 patients whose ages ranged from 2 to 14·5 years. Of the 53 defects 34 were of the foramen ovale type, eight were of the

sinus venosus type and 11 were examples of persistent common atrioventricular canal. Three patients had double lesions; of these two had both foramen ovale and sinus venosus types of lesion, and one had a foramen ovale type coupled with a persistent common atrioventricular canal. These figures do not represent the natural distribution of types of defect, for there are many atrioventricular canals still on the surgical waiting list and not shown in these figures.

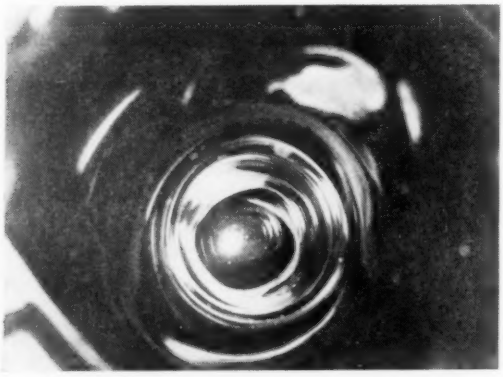

FIGURE XII.
Step V in the repair.

Of the 36 defects treated through an atrial well (in 34 patients), 22 examples of the foramen ovale type were patched and five were closed by sutures alone. Eight examples of the sinus venosus type were patched and

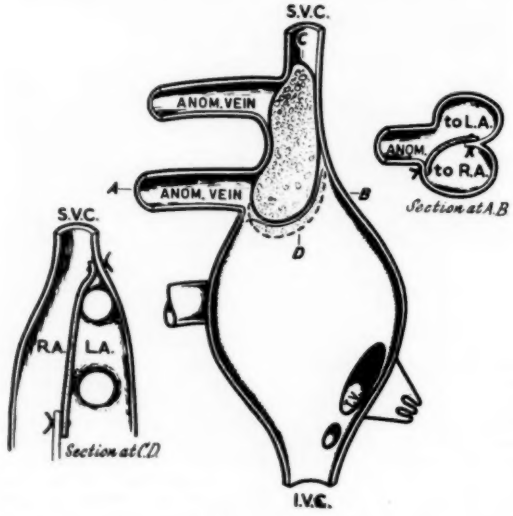

FIGURE XIII.
Patch repair of sinus venosus defect. Pulmonary venous and superior caval blood are separately channelled to the appropriate atrium by the patch.

the one example of persistent common atrioventricular canal was patched. Thus in 36 lesions, sutures alone were used in five only. In one case at the same operation open pulmonary valvotomy was performed at normal temperature with a short period of caval occlusion.

Seventeen lesions were repaired with the aid of heart-lung by-pass. Seven were of the foramen ovale type and in two of these patches were used, while in the other five sutures only were necessary. Three of the seven were considered before operation to be cases of persistent common atrioventricular canal. Of the five repaired by sutures alone, four were coincidental to other lesions—namely, Fallot's tetrad, ventricular septal defect, persistent common atrioventricular canal and pulmonary venous shunt. Ten of the 17 defects repaired with the aid of heart-lung by-pass were examples of persistent common atrioventicular canal. These are divided into Grade I (ostium primum type only—2 cases), Grade II (ostium primum type plus cleft mitral cusp—6 cases), Grade III (ostium primum type plus cleft mitral valve and cleft tricuspid valve—1 case) and Grade IV (as in III plus ventricular septal defect—1 case).

Of 34 patients operated upon with the aid of the atrial well, none died and there was minor morbidity only; one patient developed a hæmothorax, two had paroxysmal atrial tachycardia which responded rapidly to medical treatment, and two developed "post-pericardotomy syndromes", which responded to two days' treatment with bed rest and salicylates. In one case a fair result only was obtained.

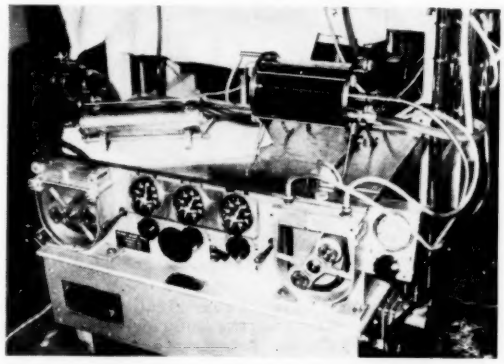

FIGURE XIV.
The rotating-disc, roller pump artificial heart-lung machine.

This child was cyanotic and had had a persistent ductus arteriosus divided two years previously. By most standards she would have been regarded as inoperable because of her pulmonary hypertension and shunt reversal. However, she tolerated operation through the atrial well very satisfactorily. It is now 13 months since her operation, which was performed at the age of 11 years. At the present time she is not cyanosed and is putting on weight, but she is still very small for her age. She has had no recurrence of her bronchitis which had troubled her frequently before. She still has some pulmonary hypertension.

After by-pass surgery two patients out of 16 died. These were children aged 2 years and 6 years respectively and in these two cases (both Grade II atrioventricular canal with severe pulmonary hypertension) the pressures in the pulmonary artery and the right ventricle were found on the operating table after repair to be the same as before. On this basis, their early death was accurately predicted. No morbidity of any significance resulted from the operation with heart-lung by-pass, but four results could be classified as "only fair". Two of these patients have residual mitral incompetence of minor degree and should not be inconvenienced. One of these had a most abnormal mitral valve, with multiple perforations instead of one orifice. In one case of the four "fair" results, heart block occurred and the fourth patient has a residual ventricular septal defect.

The heart block occurred in a boy aged 12 years, with a Grade II atrioventricular canal, a persistent left superior vena cava and an enormous coronary sinus distorting his atrial septum behind a large ostium primum defect. This boy was operated upon late in 1960 and has gone back to his own State. In recent letters he is said to be very well and back at school and his electrocardiogram is said to show

normal sinus rhythm. He has never had an episode of syncope.

A residual ventricular septal defect is present in the case of a boy, aged 3 years, with a Grade IV atrioventricular canal. In this case the posterior half of the ventricular septal defect was deliberately left unattached to the repairing patch because of the well-known danger of fatal heart block following stitches placed in this region. This accounts for his residual ventricular shunt.

The electrocardiograph gave misleading information about the nature of the defect in four patients out of 50. Three patients with the foramen ovale type of defect had left axis deviation and one with a persistent common atrioventricular canal had right axis deviation.

Summary.

Fifty cases of defect in the atrial septum are described. Sinus venosus and foramen ovale types of defect, with or without anomalous pulmonary venous drainage, have been repaired through an atrial well, with no mortality and with minimal morbidity. These patients nearly all required one unit of blood or less during their stay in hospital, got out of bed on the second post-operative day and, with few exceptions, were discharged home on the tenth day. The atrial well technique has been found to be a most satisfactory method in all cases. Later, all these patients will be screened by cardiac catheterization to determine the incidence of residual shunt.

Open heart surgery with the heart-lung machine has been reserved for those defects considered to be of the atrioventricular canal type or those in association with other abnormalities—notably the tetrad of Fallot and ventricular septal defect. The Kay-Cross heart-lung machine has been found simple and most reliable. The value of cannulæ in the left atrium and the left ventricle in the complete eradication of problems of air embolism is pointed out. Patients without complicating pulmonary hypertension can be expected to do very well indeed after this type of surgery.

References.

BROCK, R., and ROSS, D. N. (1959), "The Sinus Venosus Type of Atrial Septal Defect", *Guy's Hosp. Rep.*, 108: 291.

CAMPBELL, M., NEILL, C., and SYMONS, S. (1957), "The Prognosis of Atrial Septal Defect", *Guy's Hosp. Rep.*, 108: 1.

COOLEY, D. A., and MCNAMARA, D. G. (1958), "Ostium Primum and Atrioventricularis Communis Defects. Clinical Manifestations and Surgical Treatment", *Progr. Cardiovasc. Dis.*, 1: 89.

COOLEY, J., KIRKLIN, J. W., and HARSCHBARGER, H. G. (1957), "The Surgical Treatment of Persistent Common Atrioventricular Canal", *Surgery*, 41: 147.

DONALD, D. E. J., KIRKLIN, J. W., and GRINDLAY, J. H. (1953), "The Use of Polyvinyl Sponge Plugs in the Closure of Large Atrial Septal Defects Created Experimentally", *Proc. Mayo Clin.*, 28: 228.

EDWARDS, J., SWAN, J., WOOD, E., TOSCANO-BARBOZA, E., and KIRKLIN, J. (1956), Symposium on common atrioventricular canal, *Proc. Mayo Clin.*, 31: 509.

GROSS, R. E., POMERANZ, A. A., WATKINS, E., and GOLDSMITH, E. I. (1952), "Surgical Closure of Defects of the Interauricular Septum by Use of an Atrial Well", *New Engl. J. Med.*, 247: 455.

GROSS, R., and SAUVAGE, L. (1959), "Experimental and Clinical Studies of a Siphon-filling Disc-Oxygenator System for Complete Cardio-Pulmonary By-Pass", *Ann. Surg.*, 154: 285.

JONES, J. C. (1960), "The Results of Surgical Correction of Atrial Septal Defect Complicated by Pulmonary Hypertension", *J. thorac. Surg.*, 39: 35.

KIRKLIN, J. W., ELLIS, F. H., JUN., and BARRETT-BOYES, B. G. (1956), "Technique after Repair of Atrial Septal Defect Using the Atrial Well", *Surg. Gynec. Obstet.*, 103: 646.

KIRKLIN, J. (1960), "Arterial Cannulation for Extracorporeal Circulation using the External or Common Iliac Artery", *Surgery*, 47: 648.

MCGOON, D. C., DU SHANE, J., and KIRKLIN, J. (1959), "The Surgical Treatment of Endocardial Cushion Defects", *Surgery*, 46: 185.

MCGOON, D. C., DU SHANE, J. W., and KIRKLIN, J. W. (1959), "Surgical Treatment of Atrial Septal Defect in Children", *Pediatrics*, 24: 992.

NICKS, R., and GRANT, A. F. (1960), "The Surgery of Atrial Defects with Special Reference to the Septum Primum", MED. J. AUST., 2: 201.

STARR, A. (1960), "The Mechanism and Prevention of Air Embolism during Correction of Congenital Cleft Mitral Valve", *J. thorac. Surg.*, 39: 808.

STARR, A. (1960), "Symposium on Persistent Atrioventricular Canal", *Amer. J. Cardiol.*, 6: 565.

TOSCANO-BARBOZA, E., BRANDENBURG, R. O., and BURCHALL, H. B. (1956), "Electrocardiographic Studies of Cases of Intracardiac Malformations of the Atrioventricular Canal", *Proc. Mayo Clin.*, 31: 513.

Addendum.

Since this paper was written, 13 more children have been treated. Five had atrial septal defects patched through the atrial wall, six had atrial septal defects sewn or patched during heart-lung by-pass and two had partial atrioventricular canals repaired during by-pass. An excellent result has been obtained in all these later cases.

AORTIC STENOSIS WITH HEART FAILURE IN INFANCY.[1]

By A. W. VENABLES, M.B., B.S., M.D., M.R.A.C.P., AND PETER JONES, M.B., B.S., F.R.C.S., F.R.A.C.S., F.A.C.S.,
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HEART FAILURE is by no means uncommon in infancy. Structural lesions with abnormal mechanical loads are a frequent cause of such heart failure. Some of these lesions remain uncorrectable, and in these cases failure may represent an inevitable terminal phase. However, aortic stenosis is one of the lesions which can be relieved surgically with prospect of recovery.

Aortic stenosis causing heart failure in extreme infancy must clearly be very severe. The effect of such a lesion on the arterial pulses, and its load on the left ventricle, must be correspondingly gross and obvious.

Aortic stenosis of this severity has been described by a number of authors, some of whom merely report the phenomenon as part of the spectrum of the disease (Marquis and Logan, 1955; Bravermann and Wilson, 1957; Keith, Rowe and Vlad, 1958), while others report successful operative treatment (Abrams, 1959; Collins and Cooley, 1959).

Morgagni described stenotic aortic valves in 1791 (Willius and Keys, 1941), but it was not until 1952 that Bailey adapted Brock's pulmonary valvotomy techniques, applying them to the performance of the first transventricular valvotomy.

The years 1955 and 1956 saw the introduction of aortic valve surgery under direct vision, with the use of hypothermia and with inflow stasis obtained by means of caval occlusion. In 1959 Collins and Cooley reported successful open valvotomy in four infants aged less than six months, with cardio-pulmonary by-pass and total body perfusion.

Clinical Material.

Since 1955 three infants, presenting up to the age of 11 weeks with severe aortic stenosis and cardiac failure, have been operated on at the Royal Children's Hospital, Melbourne. One of these infants, after operation in December, 1959, is well with moderate residual stenosis and no incompetence. The other two died during or after operation.

The histories of these babies can be summarized readily (Table I). All had feeding difficulties from birth, and two were noticed by their parents to have abnormal breathing. All were in obvious cardiac failure with dyspnœa, and had cardiac and liver enlargement, but in none was this aspect of the situation appreciated by the referring doctor. In only one case was the possibility of a cardiac origin for the symptoms queried, although in another case an X-ray film had shown cardiac enlargement.

In all three infants all the peripheral arterial pulses were either impalpable or very difficult to feel, and the blood pressure was unrecordable.

In two cases no murmurs were heard initially, but all the babies were noted before operation to have obvious aortic systolic murmurs, one with an associated early systolic ejection sound. An increase in the intensity of the murmur was associated with an improvement in the child's general condition, and presumably in his cardiac output, after routine medical treatment for cardiac failure, which is described later.

[1] Read at a meeting of the Australian Pædiatric Association on April 24, 1961, at Canberra.

TABLE I.

Summary of Clinical Details of Three Reported Cases of Aortic Stenosis with Heart Failure in Infancy.

Case.	Date.	Age.	History.	Cardiac Failure.	Pulses.	Outcome of Operation.
I	December, 1955.	11 weeks.	Feeding difficulties from birth, grunting breathing. Two weeks' history of cough and cyanosis.	Present.	"Very poor."	Death.
II	November, 1959.	8 weeks.	Difficulty in feeding and a poor cry from four weeks, progressing to pallor and listlessness.	Present.	Absent.	Death.
III	December, 1959.	4 weeks.	Feeding difficulties from birth and panting breathing, progressing to frank dyspnœa on day of admission.	Present.	"Very poor."	Survival; residual aortic stenosis.

X-ray films showed the non-specific features of cardiac failure in infancy, with cardiac enlargement and some pulmonary congestion.

Electrocardiograms showed evidence of left ventricular hypertrophy and strain.

These features leave no doubt regarding the presence of gross obstruction to the left ventricular outflow tract, with consequent left ventricular overloading.

Pathological Anatomy.

In the age group under discussion such obstruction would seem almost certain to be of developmental origin.

It is important to remember that congenital aortic stenosis may be supravalvar, valvar or subvalvar. In two of the cases reported here the presence of an obstruction to the left ventricular outflow tract was confirmed by operative pressure tracings. These are ideally obtained by passing a fine catheter through the left ventricular wall into its cavity and thence into the aorta. However, the condition of a baby such as these may not permit an actual withdrawal tracing, although this should theoretically be done, if possible, to localize the site of obstruction before attempting to relieve it. In practice it may be difficult to separate a very high subvalvar obstruction from one at valve level.

Withdrawal tracings are ordinarily obtained in less severe cases of aortic stenosis by separate left ventricular puncture. This procedure provides information concerning both the site and the severity of the obstruction and may determine the actual need for surgery. In some older children with obviously severe obstruction the procedure becomes merely a planned stage of the actual operation, as in these sick infants.

Supravalvar obstruction is unlikely to be suitable for the emergency surgical procedure to be described, but both valvar stenosis and a subvalvar diaphragm should be relieved. In the two patients who died valve stenosis was demonstrated at necropsy.

Valvular stenosis has, in our experience, been due to the formation of a valve cone by cusp fusion, but it may also be due to the so-called undifferentiated aortic valve, in which obstruction is due to irregular nodular masses. These may not be improved by the technique described here.

Differential Diagnosis.

The differential diagnosis includes a variety of conditions.

Myocarditis.

If the significance of the poor pulses is misinterpreted, then the initial difficulties in hearing a murmur, which may be aggravated by respiratory noises, may lead to an erroneous diagnosis of primary myocardial dysfunction due, for example, to virus myocarditis. The electrocardiographic pattern should correct such a train of errors.

Coarctation.

Coarctation of the aorta with heart failure is associated usually with absence of the femoral pulses, but normal or full brachial pulses. Difference in quality of the femoral and brachial pulses is the cardinal sign of coarctation. This statement should not need repetition. Aortic stenosis may, of course, coexist with coarctation and may at some time require evaluation.

Diffuse Arterial Disease.

All pulses may be, and usually are, absent in the diffuse arterial disease of infancy with medial calcification. Absence of pulses is due here to the increased rigidity of the arterial wall, caused by the calcification which is visible in X-ray films of the limbs. Further, cardiac failure in this condition results from myocardial ischæmia. There is ordinarily a history of screaming attacks highly suggestive of cardiac pain, at times mistaken for the pain of intussusception. In addition the electrocardiogram reflects the myocardial ischæmia.

Paroxysmal Tachycardia.

The poor cardiac filling and consequent poor output and pulse volume of paroxysmal tachycardia should not present a real problem, nor is a moribund, pulseless phase of other conditions worthy of consideration.

Fibroelastosis.

The electrocardiogram of aortic stenosis may be reproduced identically in so-called primary subendocardial fibroelastosis of the left side of the heart with left ventricular dilatation and hypertrophy. Here the electrocardiogram shows the left ventricular strain pattern already described. However, the pulses are normal and there are usually no murmurs.

Anomalous Origin of Coronary Artery.

A rather similar electrocardiographic pattern occurs with an anomalous origin of the left coronary artery from the pulmonary artery. In this condition screaming attacks also occur owing to cardiac pain, and the electrocardiogram reflects both the left ventricular hypertrophy and the ischæmia.

In summary, the important differential diagnoses are medial arterial calcification with loss of all pulses, and fibroelastosis with its similar electrocardiographic pattern.

Management.

Our approach to pre-operative management is the same as to other cases of heart failure in infancy. Digitalization is achieved by the administration of 0·04 to 0·05 mg. of digoxin per kilogram of body weight, given intramuscularly in divided doses over 24 hours, with maintenance by an appropriate dosage of digitalis leaf.

Mersalyl is given when it is first realized that the baby is in heart failure. Sodium restriction is achieved by a diet of a low-sodium milk ("Edosol"). Broad-spectrum antibiotics are given to combat probable pulmonary infection. Oxygen is administered in a suitable cot.

The timing of surgery is dependent on the progress of the baby, and one aims at maximum improvement. This is, of course, very difficult to assess or predict. The interval between admission to hospital and surgery in this series has ranged from 15 to two days. The delay of 15 days in the first case in 1959 was related to reasonable caution in the acceptance of the proposition that such aortic valvotomy was a useful procedure.

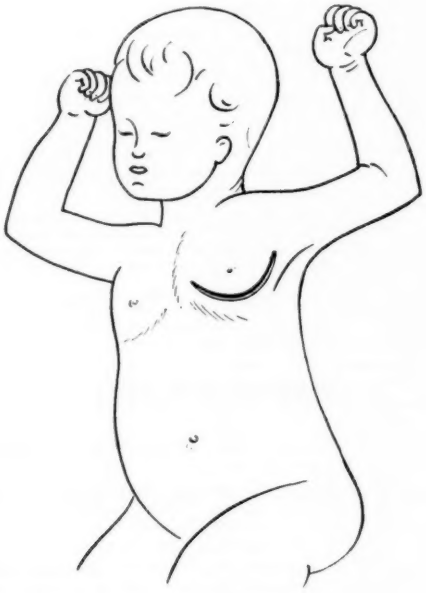

FIGURE I.
Left anterior thoracotomy incision.

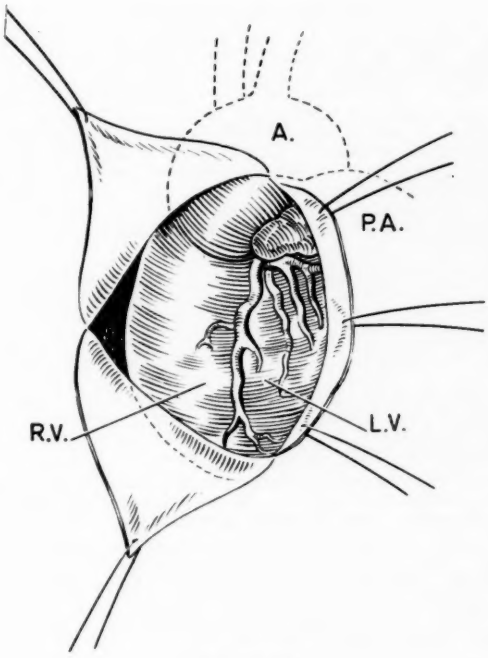

FIGURE III.
The exposure of the heart; the coronary vessel outlines the interventricular groove; A = aorta; P.A. = pulmonary artery; R.V. = right ventricle; L.V. = left ventricle.

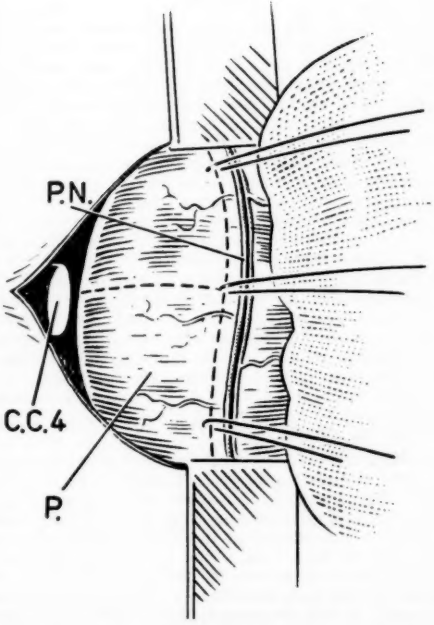

FIGURE II.
Exposure on opening thorax. The interrupted line indicates incision in pericardium (P); P.N. = phrenic nerve; CC4. = fourth costal cartilage.

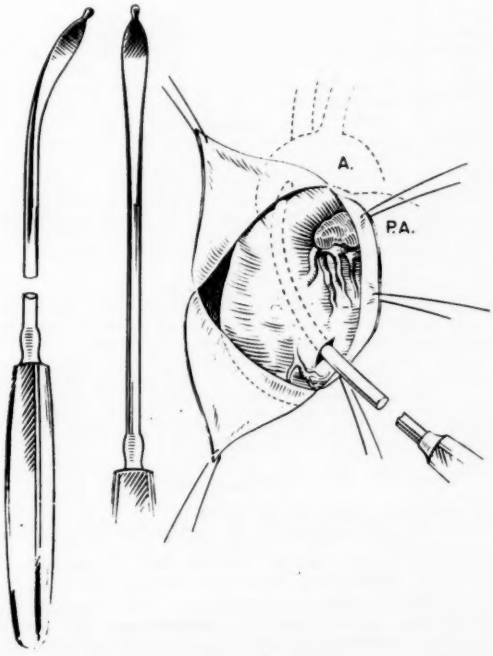

FIGURE IV.
The incision in the left ventricle is shown during the passage of an intracardiac sound. Inset is the Brock valvotome, the cutting edges adjoining the probe-pointed tip.

Operative Considerations.

The patients who have been described constitute a group whose members do not have the technical disadvantages imposed by calcification as seen in later life, but who on the other hand demonstrate the severity of their obstruction by going into myocardial failure at a very early age. Such cases pose a special problem in the selection of the best method of surgical relief. Such is the knife-edge on which cardiac output rests that even momentary occlusion of the already compromised valve orifice, by a catheter or a valvotome, may precipitate gross arrhythmia. Both bradycardia and ventricular fibrillation have been encountered.

Ideally the deformed valve should be cut carefully under vision, the surgeon bearing in mind the indefinable line between adequate valvotomy and lethal incompetence.

Transventricular valvotomy by one passage of a valvotome is a compromise between demonstrable benefit and the low reserve on which survival depends. The value of hypothermia as an adjunct is debatable, for the increased ventricular irritability which accompanies it may be the spark that fires the fibrillation inherent in the failing myocardium of aortic stenosis.

After operation digitalis should be continued until there is no tendency to cardiac failure. Minimal handling in the immediate post-operative period is essential.

Careful follow-up is necessary for the survivors, as more definitive surgery may ultimately be necessary. However, it is important to stress the life-saving nature of the procedure. One cannot over-emphasize the need for recognition of the condition, preferably early, and prior to the onset of cardiac failure.

A male infant, aged 4 weeks and weighing 3·3 kg., was operated on at normal body temperature in December, 1959. A left antero-lateral incision (Figure I) revealed a tense pericardium. A T-shaped incision (Figure II and Figure III) released a large pericardial effusion. Needle punctures showed systolic pressures to be 75 mm. of mercury in the left ventricle and 35 mm. of mercury in the aorta, where a jet of blood and an accompanying thrill were palpable. A curved sound 5 mm. in diameter was introduced through a small incision in the apex of the left ventricle (Figure IV) and passed along the outflow tract to the valve ring. With the site and direction thus established a Brock valvotome (7·5 mm. size) was then introduced in an identical direction. The cutting shoulders were felt to be held up at the valve level before passing on through the fused cusps, this manœuvre being controlled by finger-tip palpation of the valvotome from outside the aorta.

Within a few moments gross bradycardia occurred. The impending cessation of effective contractions was prevented by compression of the aortic arch by the surgeon's finger tips, the injection of 3 ml. of adrenaline solution (1: 10,000) and cardiac massage. Closure was completed without further incident.

Since operation the peripheral pulses have been palpable and the brachial pressure is now 105/90 mm. of mercury. On the seventeenth post-operative day, at the time of the patient's discharge from hospital, the chest was judged clear by clinical and radiological examination and the liver had returned to a normal size. When reviewed in February, 1961, 14 months after his operation, the child was well and active, although exhibiting signs of moderate residual aortic stenosis which will require formal elucidation by left ventricular puncture at a later date.

Summary.

Attention is drawn to the problem of aortic stenosis of extreme severity causing heart failure in early infancy.

Three cases are reported, which were treated by transventricular valvotomy; there was one survivor.

Diagnostic features are stressed. The operative technique should inflict minimal trauma and the operation should be performed at normal temperatures with skilled anæsthesia.

It is probable that this life-saving procedure will need to be followed by late reassessment and possibly formal valvuloplasty.

References.

ABRAMS, H. L. (1959), "An Approach to Biplane Cineangiocardiography", *Radiography*, 73: 531.

BAILEY, C. P. (1955), "Cardiac Surgery", Lea and Febiger, Philadelphia.

BRAVERMANN, I. B., and WILSON, S. G. (1957), "The Outlook for Children with Congenital Aortic Stenosis", *Amer. Heart J.*, 53: 487.

COLLINS, H. A., HARBERG, F. J., SOLTERO, L. R., MCNAMARA, D. G., and COOLEY, D. A. (1959), "Cardiac Surgery in the Newborn; Experience with 120 Patients under One Year of Age", *Surgery*, 45: 506.

KEITH, J. D., ROWE, R. D., and VLAD, P. (1958), "Heart Disease in Infancy and Childhood", Macmillan, New York.

MARQUIS, R. M., and LOGAN, A. (1955), "Congenital Aortic Stenosis and its Surgical Treatment", *Brit. Heart J.*, 17: 373.

WILLIUS, F. A., and KEYS, T. E. (1941), "Cardiac Classics", Kimpton, London: 184.

Reports of Cases.

COARCTATION OF THE AORTA IN INFANCY.[1]

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COARCTATION of the aorta in children is often symptomless, but it may produce cardiac failure in the neonatal period in a certain group of infants. Although rare, this is one of the commonest causes of cardiac failure in acyanotic congenital heart disease and energetic measures are necessary if these babies are to survive. The purpose of this paper is to present three infants with coarctation of the aorta who were treated by early operation.

Clinical Records.

Case I.

The patient was a full-term baby whose progress was normal until the seventh day of his life, when he became dyspnœic with feeds. On the eighth day œdema of the legs and eyelids was noticed, he refused his feeds and cyanosis of the lips was observed. Examination on the ninth day showed a pale, dusky baby with rapid respirations and inspiratory rib retraction. The liver and spleen were enlarged and there was a moderate degree of pitting œdema of the legs. There was a loud ejection systolic murmur which was maximal in the third left intercostal space. The radial pulses were easily felt, but there was no femoral pulsation. An X-ray film of the chest showed a large heart with pulmonary plethora. The electrocardiogram demonstrated slight right ventricular hypertrophy. A diagnosis of coarctation of the aorta was made and the child was given digoxin and mercaptomerin, nursed in oxygen and tube fed. A slight initial improvement occurred, but after one week of this treatment he was still in gross cardiac failure and the decision was made to operate. A venous angiocardiogram was done before operation to rule out a transposition of the great vessels. The site of the coarctation was seen, but there was no other gross abnormality. Operation was performed uneventfully on the eighteenth day of life. The ductus was patent but small.

The patient's response to operation was dramatic and within four days all evidence of cardiac failure had disappeared. Digoxin administration was stopped after seven days and he was discharged from hospital the next day. His progress since that time has been normal. The weight at eight months was 9 kg. The femoral pulses are easily felt and the blood pressure (by the flush method) is 80 mm. of mercury in the legs and 70 mm. of mercury in the arms. There is still a soft ejection systolic murmur in the chest. An X-ray film of the chest shows a normal-sized heart with slight left ventricular enlargement. An electro-

[1] Read at a meeting of the Australian Pædiatric Association on April 24, 1961, at Canberra.

cardiogram showed evidence of left ventricular hypertrophy.

Case II.

The patient, a baby boy, aged four months, had been slow to thrive, was dyspnœic with feeds and had recurrent bronchitis. Examination showed a pale, small baby with a pigeon chest and a forceful apex beat. The radial pulses were easily palpable, but the femoral pulses could not be felt. The liver was palpable three fingers' breadth below the costal margin, but there was no peripheral œdema. At the apex there was a loud pansystolic murmur and a presystolic murmur. The blood pressure (by the flush method) was 120 mm. of mercury in the arms and 50 mm. of mercury in the legs. The X-ray film of the chest showed a large heart with a prominent left atrium and pulmonary plethora. There was electrocardiographic evidence of partial right bundle branch block. A diagnosis of coarctation of the aorta with possible fibroelastosis and ventricular septal defect was made, and treatment with digoxin was given. There was no significant difference in the baby's condition as a result of this treatment and during the subsequent weeks he continued to have recurrent respiratory infections.

When he was eight months of age cardiac catheterization was performed to determine the nature of the intracardiac abnormality. There was no evidence of a left-to-right shunt, but a moderate degree of pulmonary hypertension was demonstrated, the systolic pressure in the right ventricle being 45 mm. of mercury. When he was 10 months of age the coarctation was resected. The ductus was not patent. The result of operation was a little disappointing. Although the femoral pulses were easily felt, his weight gain remained slow and his dyspnœa was little, if at all, improved. Six months after operation he is still grossly underweight, the chest deformity is unchanged and his heart size has not altered. The blood pressure is 115 mm. of mercury in the upper limbs and 95 mm. of mercury in the lower limbs. There is clinical and radiological evidence of mitral incompetence, which is no doubt responsible for the failure to improve after operation.

Case III.

A baby girl, aged three months, was found to have a systolic murmur when examined for a respiratory infection. She had been slightly dyspnœic with feeds, but the weight gain was normal. Examination showed a well-nourished baby with normal radial, but absent femoral, pulses. The blood pressure (by the flush method) was 130 mm. of mercury in the upper limbs and 70 mm. of mercury in the lower limbs. On auscultation there was a moderately loud pansystolic murmur, which was maximal in the fourth left intercostal space along the sternum. The liver was palpable three fingers' breadth below the costal margin, but there was no œdema. An X-ray film of the chest showed slight cardiac enlargement with pulmonary plethora. The electrocardiogram showed left ventricular hypertrophy. Treatment with digoxin produced slight improvement in the baby's condition, with decrease in the size of the liver and greater ability to take feeds. When she was six months of age the coarctation was resected uneventfully and at operation the ductus was found to be closed.

Since then the child's progress has been quite normal and she is symptomless. The femoral pulses are easily palpable and the blood pressure is 110 mm. of mercury in the arms and 100 mm. of mercury in the legs. She still has a pansystolic murmur in her heart which is considered to represent a small ventricular septal defect. Radiologically the heart size is unaltered.

Discussion.

Mechanically there are two factors that play a part in producing cardiac failure in infants with coarctation. The first is the presence of other cardiac abnormalities, of which patent ductus arteriosus is the commonest. Of the three patients described one had a patent ductus, one a ventricular septal defect and one mitral incompetence.

The second factor is the site of the coarctation in relationship to the ductus. A pre-ductal coarctation is more likely to produce symptoms than a post-ductal one. In practice it is difficult to be sure of this relationship at operation because of the close proximity of these structures.

The diagnosis should present no difficulty if one feels carefully for the femoral pulses. When there is doubt about the diagnosis the blood pressure should be taken by the flush method in upper and lower limbs with the child well sedated. A difference of more than 20 mm. of mercury is significant, and in the group of patients with cardiac failure it is not unusual to find a gradient of 60 mm. or more. In the two cases in which this measurement was made before operation the gradients were 70 mm. and 60 mm. of mercury respectively.

There is no unanimity about the method of treatment of this group. Nadas (1957) advocates energetic medical treatment and claims good results when digoxin is given over long periods. He advises operation when the patient is aged five to seven years. Glass, Mustard and Keith (1960), on the other hand, favour early surgery, particularly if the cardiac failure does not respond rapidly to medical treatment or if failure develops in the first two weeks of life. The main objection to early surgery is the high operative mortality. However, none of our reported patients gave rise to any anxiety. The other objection is that the anastomosis may not grow with increasing age and a second operation may be necessary at a later date. Experimental evidence and follow-up studies suggest that subsequent operations on the anastomotic site should not be necessary. It would be foolish to draw conclusions from three cases, but the effectiveness and comparative safety of early surgery have been demonstrated.

Summary.

Three babies with coarctation of the aorta are presented, in whom operation was performed in the first year of life. The factors in the early onset of cardiac failure are mentioned and the methods of treatment discussed briefly.

References.

NADAS, A. S. (1957), "Pediatric Cardiology", Saunders, Philadelphia and London: 386.

GLASS, I. H., MUSTARD, W. T., and KEITH, J. D. (1960), "Coarctation of the Aorta in Infants", *Pediatrics*, 26: 109.

CHOLEDOCHAL CYST.[1]

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THE unusual event of three cases of choledochal cyst presenting for surgery in two and a half years prompts this report. Although there have been frequent references to the condition in medical literature since it was first reported by Vater in 1793, it is very rare. Judd and Green found only one case in over 17,000 operations on the biliary tract at the Mayo Clinic. Sir James Walton of London was one of the few authors to describe two cases of his own. He stated that they were the only two cases seen among 23,000 necropsies at the London Hospital in 32 years prior to 1938.

The condition consists of a localized dilatation of part or the whole of the common bile duct. Unlike that due to obstruction, the dilatation does not extend throughout the whole biliary system and the gall-bladder and cystic duct are of normal size. It is not a diverticulum, but an aneurysm, and is explained by Yotuyanagi as a disturbance of the rate of epithelial proliferation during a stage of fœtal development, causing one segment to grow to a greater diameter.

[1] Read at a meeting of the Australian Pædiatric Association on April 21, 1961, at Canberra.

The cyst wall, often surprisingly thin, is composed of fibrous tissue with occasional elastic fibres and smooth muscle elements. The lining epithelium, which may be cuboidal, is often absent if there has been marked inflammation.

Because it is fixed distally by the common bile duct and proximally by the hepatic duct, and is bounded in front by the liver and behind by the vertebral column, the cyst can only enlarge downwards, forwards and to the right. Perhaps the weight of contained bile produces a flap or valve which is effective only when the cyst is partly distended, being released when the cyst becomes tense; this empties the sac for another cycle of filling and accounts for the intermittency of the jaundice. Chronicity and intermittency are noteworthy features.

Typical clinical features are a mass, pain, vomiting and jaundice.

Ravitch reviewed the medical literature on the subject with special reference to similar work by Tsardakas and Robnett. A mass occurred in over 70% of these cases, its size and tenseness varying from time to time, and it often simulated liver enlargement.

Pain occurred in the right upper quadrant of the abdomen in over 60% of cases and was often the only symptom. It could be cramping or colicky pain, or merely heavy pressure or discomfort.

Vomiting occurred when the cyst was sufficiently large to press upon and obstruct the duodenum.

In 70% of cases jaundice was present, which was characteristically intermittent. This was generally associated with the passage of acholic stools and dark urine.

Bouts of infection and ascending cholangitis during obstructive episodes resulted in superadded chills and fever.

Gross stated that there was an average delay of three years between the first complaint and the making of the diagnosis.

The total number of cases reported was 242 in 1957.

Eighty *per centum* occurred in females. Sixty *per centum* of patients were under 10 years of age when the condition was discovered, but patients were usually over three years of age.

Differential Diagnosis.

The differential diagnosis includes any other cause of abdominal pain, mass or jaundice.

Abdominal neoplasms, such as Wilms' tumours or neuroblastomas, are more often irregular in outline and have a firm consistency. Jaundice is a late phenomenon. Hydatid cysts, pancreatic cysts, renal cysts, congenital cysts of the liver, mesenteric cysts and intestinal duplications are generally mobile and painless, and do not cause jaundice.

On radiological examination one may see (i) a rounded, soft-tissue mass, often with the renal shadow centrally superimposed (sometimes calcification occurs in the cyst wall and McLachlan states that air within the cyst is pathognomonic); (ii) a displaced, compressed duodenum flattened against the anterior abdominal wall after a barium meal; (iii) a non-visualized gall bladder after intravenous cholecystography.

Treatment.

A high mortality rate (20%-30%) exists because in many cases a pre-operative diagnosis has not been made, and there has been attempted radical removal of the cyst, or else confusion has existed on the part of the surgeon as to the correct procedure.

Treatment should consist of the reconstitution of adequate communication between the biliary system and the gastrointestinal tract, either by a Roux-en-Y choledocho-jejunostomy (Figure I) or by direct anastomosis (Figure II) between the cyst and the duodenum, which Gross and others state is perfectly satisfactory, but which has the theoretical possibility, at any rate, of ascending infection and cholangitis. Experimental work by Gentile indicates that this danger in the absence of biliary stasis is exaggerated. Two post-mortem examinations done several years after operation confirm this. McWhirter quotes one autopsy performed 13 years after operation with no evidence of ascending infection or cirrhosis. The great shrinkage of the cyst after operation is also noteworthy. Ravitch holds that the Roux-en-Y operation is feasible only when there is a very large cyst. In smaller ones, which

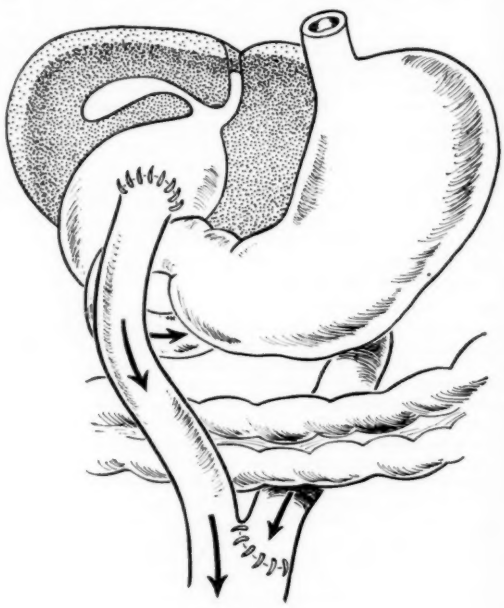

FIGURE I.
Roux-en-Y choledocho-jejunostomy.

are essentially retroduodenal and densely adherent to the duodenum, it is to be feared that the long limb of the anastomosis may compress the duodenum as it crosses it. Also the two anastomoses in the case of the Roux-en-Y operation must carry more operative and post-operative risk because of the longer time taken and a greater tendency to intestinal obstruction or anastomotic leak.

In addition to the danger of subsequent cholangitis there is a marked tendency to stenosis of the stoma with obstructive symptoms. Therefore the anastomotic opening must be large initially.

Case I.

The patient was a boy, aged five months. He had been perfectly well until four days before admission to hospital, when he commenced vomiting, intermittently at first but later copiously. He had no abdominal pain. He had been oliguric for 24 hours, and had passed loose stools, which were not clay-coloured.

His extremities were cold and there was a poor peripheral return of circulation. Tachycardia was present. He was tender in the right hypochondrium, but no mass was palpable and he was not jaundiced.

A provisional diagnosis of gastro-enteritis or intermittent intestinal obstruction from volvulus was made.

He was adequately resuscitated with fluids given intravenously, but seven days later, while he was still in hospital, an ill-defined, somewhat cystic mass was felt. This was not ballottable in the loin and appeared anteriorly situated.

A provisional diagnosis of intussusception was made.

At operation a choledochal cyst was discovered. Direct anastomosis to the duodenum was performed and convalescence was uneventful.

Case II.

The patient was a girl, aged 21 months. She had been perfectly well until three weeks previously, when she had a vomiting attack and passed loose, yellow stools. A week later a further vomiting attack occurred, associated with severe abdominal pain. She was then listless and anorexic. A week subsequently her mother noticed her distended abdomen. Her pains persisted.

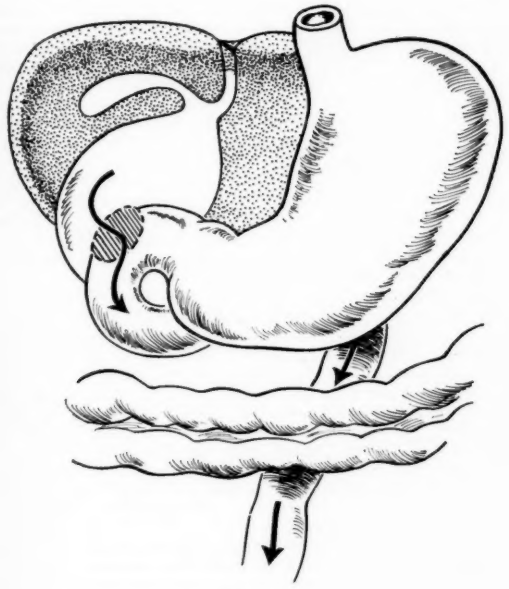

FIGURE II.
Direct anastomosis.

Her stools were normal and she was not jaundiced, but her urine was observed to contain bile when it was tested in the ward, although it was not noticeably dark. A large, hard abdominal mass was ballottable and a provisional diagnosis of Wilms' tumour was made. An X-ray film showed a renal outline in the midst of the abdominal mass and a lateral view of the intravenous pyelogram showed the mass to be anterior to the kidney.

A Roux-en-Y choledochojejunostomy was performed, resulting in cure of her symptoms.

Case III.

The patient was a girl, aged five and a half years. She was said to have had hepatitis when aged 18 months. This recurred 12 months later and she had had intermittent jaundice since. In spite of this she had been well until one month previously, when she became anorexic; her urine became dark in colour and her motions pale. Her sclerotics were yellow. Progressive distension of her abdomen was noticed, and a firm liver, palpable four fingers' breadth below the costal margin, was recorded. Her spleen was not palpable.

A provisional diagnostis of chronic hepatitis was made, but the results of investigations were as follows. The total serum bilirubin level was 2·3 mg. per 100 ml.; the directly-acting serum bilirubin level was 1·4 mg. per 100 ml.; the indirectly-acting serum bilirubin level was 0·9 mg. per 100 ml.; the thymol turbidity reading was 2 units; no abnormality was detected in the serum transaminase; the Casoni test gave a negative result.

A direct anastomosis between the cyst and the duodenum was performed.

Bibliography.

FIDDIAN, R. V., and MCDOUGALL, C. (1959), "Choledochus Cyst", *Brit. J. Surg.*, 47: 240.

HANKAMP, L. J. (1959), "Congenital Choledochal Cyst; Demonstration by Oral Cholecystography", *J. Dis. Child.*, 97: 97.

HORNE, L. M. (1957), "Congenital Choledochal Cysts", *J. Pediat.*, 50: 30.

NEWSON, A. L. (1952), "Congenital Cystic Dilatation of the Common Bile Duct", MED. J. AUST., 1: 784.

RAVITCH, M. M., and SNYDER, G. B. (1958), "Congenital Cystic Dilatation of the Common Bile Duct", *Surgery*, 44: 752.

TSARDAKAS, E. N., and ROBNETT, A. D. (1956), "Congenital Cystic Dilatation of the Common Bile Duct", *Arch. Surg.*, 72: 311.

Medical Surveys.

CANCER CHEMOTHERAPY: PART TWO.

Antimetabolites.

Folic Acid Antagonists.

History.—In work on transplanted and spontaneous tumours in mice, Lewisohn (1938) observed regression of sarcoma 180 with extracts of beef spleen, and regression of spontaneous breast carcinoma with mouse spleen. Since it was not practicable to harvest mouse spleens on a large scale, other sources of the same compounds were investigated; extracts of barley and brewer's yeast appeared to cause the same regression of mouse breast carcinoma, and this material was refined until the group could report (Leuchtenberger *et alii*, 1945) complete regression of 30% of breast carcinoma in three strains of mice with the *Lactobacillus casei* fermentation factor (subsequently identified as pteroyl triglutamic acid, a conjugate of folic acid). Clinical trials began with various folic acid conjugates (Farber *et alii*, 1947; Lehv *et alii*, 1948) showing negligible objective improvement. However, Farber observed that the course of acute leukæmia had in fact been accelerated by folic acid and its conjugates (Farber, 1949), so folic acid antagonists were synthesized by Hutchings *et alii* (1947) and Seeger *et alii* (1947) in an attempt to induce the opposite effect of inhibition of leukæmia. Clinical and hæmatological remissions of acute leukæmia were obtained by Farber *et alii* (1948) and Dameshek (1948, 1949) using the folic acid analogues "Aminopterin", α-methopterin and amino-an-fol. In subsequent studies "Amethopterin" (methotrexate) has been successful with breast carcinoma (Wright *et alii*, 1959), choriocarcinoma (Hertz *et alii*, 1958), Hodgkin's disease, multiple myeloma and many other malignant tumours (Wright *et alii*, 1951).

Mechanisms of Action.—Folic acid and its biologically active form, the citrovorum factor (Sauberlich and Bauman, 1948) are essential nutritional factors present in all tissues, but in highest concentration in tissues in a state of rapid growth. Substitutions have been made at various sites, but we shall consider only "Amethopterin" (methotrexate), the folic acid antagonist in widest use for its anti-tumour activity and low toxicity, with its two substitutions to form 4-amino-N^{10} methyl-pteroyl glutamic acid. The folic acid antagonists produce effects in animals similar to folic acid deficiencies brought on by restricted diet—hypoplasia of bone marrow, thymus and spleen, weight loss, anorexia, diarrhœa and adrenal hyperplasia—and these are reversible by folic acid or the citrovorum factor (Oleson *et alii*, 1948). They would appear to act on Woods' (1940) principle of competitive inhibition, but neither the inhibitory effect on tumour growth nor the toxicity can be reversed by simultaneous administration of folic acid; however, the marrow toxicity can be reduced by simultaneous administration of citrovorum factor (folinic acid) and clinical trials of this combined therapy are in hand (Wright, unpublished). Other mechanisms of action are possible through endocrine functions, for they can prevent metamorphosis in *Drosophila megalogaster* (Goldsmith *et alii*, 1948), impair reproduction in pregnant rats (Nelson and Evans, 1949), and cause failure

of the animal or animal tissue to respond to œstrogens (Hertz, 1948; Brendler, 1949). The female mouse is more tolerant of the drugs than the male (Schoenbach, 1950). Further, adrenal hyperplasia is caused by the drugs; the effects on spleen, peripheral blood and marrow are less in the rat after adrenalectomy (Higgins and Wood, 1949); urinary corticosteroid levels fall in the leukæmic patient treated with folic acid antagonists (Schoenbach, 1950); the eosinophil level frequently falls (Wright, 1952); and remissions in rheumatoid arthritis and psoriasis have been observed (Gubner *et alii*, 1951). Interference with the conversion of folic acid to the citrovorum factor (folinic acid) has been suggested (Nichol and Welch, 1950; Schoenbach *et alii*, 1950). It is significant that tissue culture techniques demonstrate cytotoxic activity of the drugs *in vitro*—that is, independent of hormonal systems (Antikajian *et alii*, 1951; Plummer, 1952).

Toxicity.—The toxic effects of folic acid antagonists are essentially similar to the effects of dietary folic acid deprivation, and affect principally the gastro-intestinal tract and the bone marrow (Wright *et alii*, 1951). In the gastro-intestinal tract nausea, vomiting, epigastric pain, diarrhœa and sometimes bleeding can be produced. The bone marrow effects are leukopenia and platelet depletion. Ulceration of surface epithelium frequently occurs in the mouth and vulva, and a drug rash is common. The toxic effects can be reversed with the citrovorum factor administered as 3 mg. intramuscularly daily, but not by folic acid. However, in one patient described by Hertz (1958), acute toxic hepatitis with death occurred, and he regards impaired liver function as a contraindication to intensive courses of therapy.

Administration and Dosage.—"Amethopterin" (methotrexate) is dispensed as a tablet of 2·5 mg., and in injectable form. The oral dose of 2·5 to 10 mg. is usually given daily. Hertz *et alii* (1958) used five-day courses of 10 to 30 mg., usually given intramuscularly, but sometimes by the continuous intravenous drip method. Whiteside *et alii* (1958) have successfully used the drug intrathecally at a dose rate of 0·1 to 0·5 mg. per kilogram of body weight. As with other cancer chemotherapy drugs it is difficult to maintain high dosage levels, for leukopenia results as a side effect, especially in older patients. Since the timing and degree of bone-marrow depression are unpredictable, white-cell counts must be performed at weekly intervals before the next dose is prescribed; and further treatment is delayed if the total white-cell count is below 5000 cells per cubic millimetre.

Purine and Pyrimidine Antagonists.

Since purines and pyrimidines are structural constituents of nucleic acids, the substitution of an altered form is intended to compete with those purines and pyrimidines normally incorporated into nucleic acids. The deoxyribonucleic acid formed with this false member would not be expected to replicate successfully. Since the neoplastic cells are undergoing cell division at a rate in excess of most normal cells, such an effect should be seen earliest in these malignant cells. Various analogues of purines have been synthesized in the attempt, and of these, 6-mercaptopurine continues in use for its effect on acute leukæmia.

Mercaptopurine.—Hitchings *et alii* (1950) described the synthesis and biological properties of 6-substituted purines. Mercaptopurine is an analogue of adenine and hypoxanthine, and microbiological studies (Elion and Hitchings, 1953) show it to be an antagonist to both. Burchenal *et alii* (1953) demonstrated its anti-leukæmic activity in man. Various reports since then, including those at a conference on the drug (Burchenal *et alii*, 1954; Hall *et alii*, 1954), have confirmed the value of 6-mercaptopurine in acute leukæmia and chronic myeloid leukæmia, but the drug has not been effective in other forms of malignant disease. Toxicity on white-cell and platelet production are high, and bleeding is a common complication of therapy. The drug is given orally at the rate of 2·5 mg. per kilogram of body weight daily and continuously. Since the marrow depression can be delayed, treatment should be stopped when the white-cell count first begins to fall, but may be resumed if the white-cell counts stay stable for more than four days. In experimental testing, 6-selenium purine has shown no advantage over 6-mercaptopurine.

Fluorouracil.—In 1957 Heidelberger described a new pyrimidine analogue, designated 5-fluoro-uracil (5FU). When it is labelled with ^{14}C its incorporation into ribonucleic acid has been demonstrated, and also its localization in one carcinoma of the lung. The drug is absorbed orally intact within 20 minutes, and in the first 24 hours 20% appears in the urine as unchanged fluoro-uracil, while 25% of the radioactivity is respired as carbon dioxide (Heidelberger *et alii*, 1958). The drug is given by mouth or intravenously at the rate of 4 to 8 mg. per kilogram of body weight daily. At the upper dose levels toxicity develops in the gastro-intestinal tract (with diarrhœa, abdominal pain and vomiting) and in the marrow (with thrombocytopenia and leukopenia) (Hall, 1958). Ansfield and Curreri (1958) found that in all patients whose tumours regressed the dosage had been pushed to toxic levels. Interest has been maintained in this agent in that some bowel carcinomas have responded, for these are commonly resistant to other drugs, and Curreri (1959) has been using 5FU at a dose rate of 15 mg. per kilogram for three days as an adjuvant to major bowel surgery. In inhibiting various mouse leukæmias and reticuloses 5-fluorodeoxycytidine and 5-fluorouridine have been equally as effective as 5-fluorouracil (and these effects were much more consistent than those induced by anti-folic, anti-purine and anti-glutamine compounds), but other fluorinated pyrimidines, such as 5-fluoroorotic acid and 5-fluorocytosine were ineffective (Law, 1958). Three other compounds, 6-thioguanine, 5-azaguanine and thioguanosine, all effective against experimental tumours, are presently undergoing further clinical trials (Schroeder, 1959; Brockman *et alii*, 1959; Krakoff *et alii*, 1959). The number of these clinical substitutes under investigation by laboratory and clinical workers reflects the intense interest in the possibilities that these interpolations into the very centre of the genetic and enzymatic control of the cell will wreck it. It will require a nice degree of chemical precision to localize the wrecking process to malignant cells.

Antibiotics.

Those antibiotics shown to be effective against malignant disease have all been products of fungi. They are actinomycin, mitomycin, puromycin and azaserine.

Actinomycin.

Actinomycin was isolated from a culture of soil actinomyces by Waksman and Woodruff in 1940, and actinomycin D from cultures of *Streptomyces parvallus* in the same laboratories by Manaker *et alii*, in 1954. Animal studies by Farber (1955) demonstrated its anti-tumour activity, and clinical studies (Farber *et alii*, 1956; Golomb *et alii*, 1957) have indicated its possible usefulness. In her tissue culture studies on the effects of actinomycin D on normal and neoplastic cells, Cobb (1958) found that primary cultures were much more sensitive than those of established cell lines, that the response was not predictable according to pathological cell type and that no correlation could be made with the effects of other cytotoxic drugs. The mechanism of action was indicated as inhibition of pantothenate utilization, suggesting interference with synthesis and/or biological activity of coenzyme A.

Sporadic remissions have been achieved in various tumours, but more frequent effects have been demonstrated in children on rhabdomyosarcoma and on Wilms' tumour, especially when combined with radiotherapy (Farber, 1956; Tan *et alii*, 1959). Moore *et alii* (1958) ran a clinical trial in which 75 γ per kilogram were given as a five or ten-day course to 71 patients, and concluded that actinomycin D was not a clinically effective agent for patients with advanced adenocarcinoma; but Pinkel (1958), from the same clinic, achieved good remissions in sarcoma in children, using a dose of 2·4 mg. per square metre of

body surface area. Tan's parenteral course is 15 γ per kilogram daily for five days.

The toxic effects observed are anorexia, nausea and vomiting, which can be controlled by chlorpromazine given before the drug. Oral toxic effects with ulcerative stomatitis are common in children, and depression of platelet and white-cell production occurs. Intravenous injection is necessary and extravasation can produce severe irritation.

A further derivative, actinomycin P_2, appears effective against the same marrow spectrum as actinomycin, and its combination with X-ray therapy is under study (Medrek, 1961).

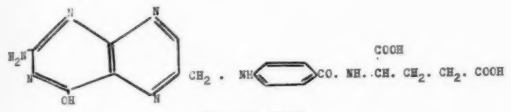

FIGURE VIII.
Pteroyl glutamic acid (folic acid).

Mitomycin.

In 1955 Hata in Tokyo isolated a group of antibiotics produced by a new strain, *Strep. cæspitosus*. Of the fractions of these, mitomycin C (also known as mitomycin X) was found to be effective against malignant tumours (Hata *et alii*, 1957), and this was confirmed by Suguira and Stock (1958).

The drug has been refined to a stable, crystalline form, and is administered parenterally, usually intravenously, at the rate of 40 γ per kilogram of body weight daily. The usual dose is 1 to 5 mg. Intraarterial injection through an indwelling "Polythene" tube is regarded by Shiraha as the method of choice.

Shiraha *et alii* (1960) reported improvement in a wide variety of malignant states, including adenocarcinomas in bowel, with regression of the tumour in some 25% of patients.

The principal side-effect is leukopenia, which disappears within three weeks of cessation of the drug.

Puromycin.

Puromycin ("Stylomycin") is an antibiotic derived from a species of actinomycete, *Strep. albo-niger*, by Hesseltine *et alii* (1954). This agent and its amino-nucleoside were found to have activity against some animal tumours (Troy *et alii*, 1954), but have been disappointing in clinical use (Wright *et alii*, 1955).

The dose rate is 250 to 1000 mg. given orally daily. The side effects observed were nausea, vomiting and diarrhœa, but no significant affection of bone marrow.

The mode of action is apparently by purine antagonism (Oleson *et alii*, 1955).

Azaserine.

Azaserine, a diazo-acetyl serine derived from a streptomyces, acts as a glutamine antagonist (Hartman *et alii*, 1955), and has produced temporary remission in leukæmia alone, and in combination with 6-mercaptopurine. As with puromycin, azaserine is no longer in clinical use.

Other Antibiotics.

Other antibiotics and their derivatives are under study, such as "Sanamycin", streptovitacin, E73, carzinophillin, duazomycin A, mithramycin, streptonigrin and carbomycin. Levi *et alii* (1960) have reported experimental success with a derivative of chloramphenicol. McLeay *et alii* (1960) have shown by fluorescent techniques that tetracycline is concentrated in rapidly-growing and malignant tissue, and have used this antibiotic as a vehicle for ^{131}I for diagnostic and therapeutic purposes in animals.

Other Agents.

The laboratory and clinical testing of new cytotoxic agents has been growing on such a vast scale that it is not possible to deal adequately with all the drugs in present use. Two agents in long use and repeatedly revived are urethane and colchicine.

Urethane.

Haddow and Sexton (1946) systematically examined the effect on the growth of experimental tumours of all drugs reported to have effects on mitosis. Phenylurethane and its derivatives were studied because plant physiologists had shown its effect as a weed killer in arresting mitosis in roots.

Urethane, long in use as a laboratory anæsthetic agent, was found to inhibit mouse breast carcinoma and Walker rat carcinoma.

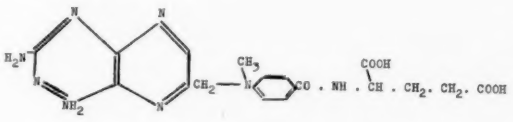

FIGURE IX.
4-amino-N^{10} methyl-pteroyl glutamic acid ("Amethopterin", methotrexate).

The mode of action of urethane is unknown, but it has been shown to have a mutagenic action, to produce mitotic disturbances, and to damage liver capillaries. It is also carcinogenic in producing experimental lung carcinoma, and is an initiating factor in skin carcinogenesis.

In clinical practice, the depressive effect on white cells led to its use in leukæmia. Paterson (1946) and Berman and Axelrod (1948) reported a high frequency of remission in chronic myeloid and lymphoid leukæmia, though no effect on acute leukæmia was found. Huggins (1947) found objective and subjective evidence of remission of prostatic carcinoma which was not mediated through hormonal stimulation. Loge and Rundles obtained marked improvement in patients with multiple myeloma.

The dose is 2 to 4 grammes per day by mouth.

The toxic effects are nausea, vomiting and marrow depression.

Colchicine.

Colchicine has long been known as an inhibitor of mitosis, but produces no clinical remissions of tumour growth. Derivatives such as desacetylmethylcolchicine have been under trial, since Leonard and Wilkinson (1955) showed remission in chronic myeloid leukæmia, but Scott (1958) has found it a difficult drug to manage, with frequent toxic side-effects.

THE FUTURE.

Extension of Present Drugs.

In many ways the usefulness of the agents presently at hand has been and can be extended. In the endeavour to increase the drug dosage to the tumour, the concentration of the drug at the tumour is raised, and so also may the time for which the drug is presented directly to the tumour.

First, the concentration of the drug at the site of the tumour can be raised by such techniques as intracavitary injection into the pleura and peritoneum; by injection into the arteries of the region at intervals; by direct injection into tumour nodules; and by repeated recirculation through the tumour area by an isolated perfusion technique. Until drugs are developed which are selectively taken up by tumour cells, the effective increase in dosage within the tumour cell will be uncertain. Injections into the region of the tumour cells will not necessarily raise the intracellular drug concentration if the drug is removed via lymphatic or venous channels from that site without ever entering the target cells. Intraarterial injections and perfusion methods are more likely to deliver the drug along the correct highway, but are diluted in passing

through the whole area served by that circulation. That drug fixation occurs is suggested by the lower systemic toxicity after intraarterial and perfusion methods, when rapidly-fixed drugs such as nitrogen mustard are given.

Second, the time for which the drug is in contact with the tumour can be increased by repeated dosage, but this is limited by toxicity to the bone marrow. The bone marrow can be mainly excluded by regional perfusion, and recirculation of the agent through the tumour-bearing area can be continued for about half an hour. Since the tumour cells are most sensitive during division, perfusion techniques are being extended to longer periods experimentally in an attempt to include the division time of

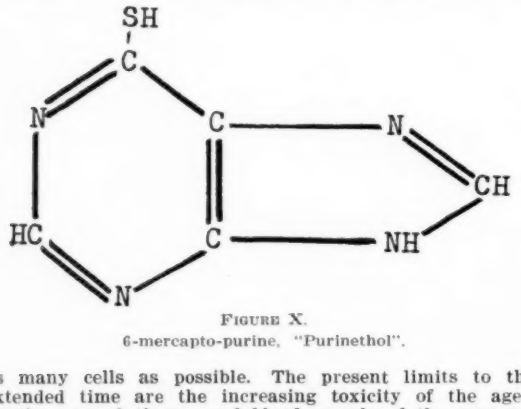

FIGURE X.
6-mercapto-purine, "Purinethol".

as many cells as possible. The present limits to this extended time are the increasing toxicity of the agent on the normal tissues and blood vessels of the area perfused resulting in skin and muscle death with œdema and thrombosis, the inability to maintain isolation of the area by tourniquet over longer periods and the local ischæmic effects of the tourniquet. However it is possible to leave the arterial and venous cannulæ in place so that repeated infusion is possible, with the limit then of drug leakage through collateral circulation to the sensitive marrow. Attempts have been made to increase the mitotic rate during the time of perfusion to raise the proportion of cells in their vulnerable phase. The methods have included tri-iodo-thyronine administration, heating of the perfused blood, and raising of the oxygen tension of the perfused blood. Assessment of these adjuvants is not yet possible, but certainly no dramatic positive results have followed in clinical practice.

Third, the toxicity of the drugs may be reduced when more specific cancericidal drugs are developed. Meanwhile certain antidotes are available only for the folic acid antagonists. Citrovorum factor (folinic acid) given simultaneously with "Amethopterin" reduces toxicity, but apparently not the tumour inhibitory effect. The technique for using anti-metabolite-metabolite combinations is well established (Sullivan *et alii*, 1959). The anti-metabolite is delivered continuously for five to seven days through a fine polyethylene intraarterial catheter directed as accurately as possible to the tumour. The protecting metabolite is given simultaneously by intermittent intramuscular injection. Herter *et alii* (1960) report some success with this technique using "Amethopterin" with citrovorum factor or 6-amino-nicotinamide. When the mechanisms of action of the alkylating and other agents on the marrow are more exactly defined, it may be possible to provide a metabolite simultaneously which will protect those normal cells. Ross *et alii* (1960) have reported excellent protection from marrow depression in animals and humans using intravenous sodium thiosulphate intravenously during the time of HN2 administration.

In the meantime it is possible to separate the drug from the marrow by regional perfusion, or the marrow from the drug by prior marrow aspiration and storage with reinfusion of the marrow after the drug has been wholly inactivated or excreted (McFarland *et alii*, 1959; Jones *et alii*, 1960). This technique is being exploited in conjunction with regional perfusion when the drug leakage from the isolated perfusion circuit is unpredictable, or known to be large. When marrow storage is better developed it is conceivable that marrow proliferation *in vitro* can be encouraged by tissue culture techniques to provide individual marrow banks for patients having large or repeated doses of radiotherapy or radiomimetic drugs.

White (1959) has shown experimentally that systemic toxicity from nitrogen mustard is sharply reduced by prior splenectomy, and this has been exploited surgically by splenic exclusion during the period of activity of

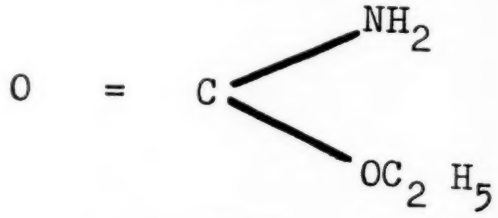

FIGURE XI.
Ethyl carbamate, urethane.

administered mustard. However, Demetz *et alii* (1960) could show no reduction of marrow depression by temporary splenic exclusion, or by replacement of fragmented or homogenized spleen into the peritoneum.

Fourth, more exact tumour-drug selection is possible. At present previous clinical experience is the guide, but selection is quite empirical. Correlation studies (Wright *et alii*, 1959) between clinical and tissue culture sensitivities of the same human tumour have shown close agreement, and this screening method can be extended. The hamster cheek-pouch method of Adams (1959) can be used, in which a human tumour is transplanted to a hamster and maintained with the aid of cortisone — here the tumour can be tested *in vivo* against various drugs.

Fifth, the drugs can be used in association with primary and secondary surgery, to exploit their usefulness in destroying small clumps of unestablished tumour cells. Kondo *et alii* (1958) have given experimental evidence that small clumps of tumour cells, such as are forced into circulation at the time of surgery, can be destroyed by an appropriate chemotherapeutic agent. It was also observed that cortisone, operative trauma, and ineffective chemotherapeutic agents might cause an increase in the number of viable metastases.

Nitrogen mustard, at least, does not appear to interfere with healing after operation, including the healing of the bronchial stump after pneumonectomy (Ross and Mashatt, 1958). Brown *et alii* (1959) found nitrogen mustard to be the most effective tumoricidal agent when used topically, and found little interference with wound healing. Cole (1958) has shown that nitrogen mustard effectively destroyed free tumour cells in the lumen of the gut at the time of colonic resection, being equally as efficient as the perchloride of mercury advocated by Naughton Morgan to reduce the rate of tumour recurrence at the suture line.

Conflicting reports have appeared on the efficacy of "Clorpactin" in controlling tumour spread at operation. Atik *et alii* (1960) were unable to show any cancericidal effect of peritoneal irrigation with "Clorpactin" after deliberate spillage of tumour particles into the peritoneum in rabbits. Shapiro (1958) has shown experimental evidence that adjuvant chemotherapy can permit cure of residual tumour after partial excision.

Warren Cole in Chicago (McDonald *et alii*, 1957; Collier *et alii*, 1959) has almost completed a double-blind trial of adjuvant chemotherapy used at the time of primary abdominal surgery for cancer, and a further large-scale

cooperative study in some 48 departments of surgery is presently in progress (Shimkin and Moore, 1958). The information from this extensive clinical trial will be extremely valuable in assessing the value of complementary chemotherapy.

Sixth, agents which apparently produce their effect in different ways can be combined (Skipper *et alii*, 1954; Bagshawe and McDonald, 1960). The rationale is similar to that of double anti-bacterial agents used simultaneously to limit the emergence of strains resistant to either. In this context Watson and Turner (1959) have combined TSPA with testosterone in the treatment of advanced breast tumour, and similarly Holden and Sundstrup (1959) using TSPA with fluoxymestrone.

Even tumours which have previously responded develop drug resistance eventually; and Murphy *et alii* (1954) have shown that leukæmia, previously sensitive to "Amethopterin", acquires cross-resistance to all other folic acid antagonists. However, Li *et alii* (1959) were able to reduce chorionic gonadotrophic hormone excretion to normal in a patient with "Amethopterin"-resistant choriocarcinoma using actinomycin D.

Further, Brennan and Vaitkevicius (1959) observed apparent potentiation of effects of 5-fluorouracil on various solid tumours when combined with 6-mercaptopurine, and Ryan *et alii* (1960) found potentiation of HN2 by colchicine.

Seventh, the worth of various agents in present use is being clarified by careful, controlled clinical trials. For various reasons, including the rapid appearance of new drugs to be tested, such trials must be completed quickly. To test an adequate number of patients, many centres combine their material and work to exact criteria of selection and treatment to ensure that reliable information results from this concentrated experience. Such a trial is presently evaluating the efficacy of 6-mercaptopurine in acute leukæmia. Many difficulties harass the organizers of such trials, not least that the patients treated are limited to those in whom no hope of cure or successful palliation is offered by conventional methods. The production of agents with more predictable effects will allow clinical trials to be conducted on a wider range of degrees of disease, especially on different diseases from the reticuloses.

New Drugs.

The energy and effort presently employed in finding and testing new agents are immense.

The derivation of the agents is either entirely empirical (as in the culturing of soil samples taken all over the world), or systematically empirical (as in the repeated substitutions within the chemical structure of known sporadically effective compounds) or hopefully empirical (as in the production of "tailor-made" compounds—for example, the phenylalanine chain added to the mustard entity or the acetylation of the DNA of the patient's own tumour).

This congeries of compounds presenting for testing has induced various screening techniques intended to limit wasted effort in the trials on human malignant disease; for chemists can create compounds faster than biologists can test them.

Microbiological screening methods test the effects of new agents on various bacterial, fungal and protozoan systems growing in controlled media. The inhibition of growth in any particular system can indicate the blocking of one metabolic pathway. That is, each microbiological system used is designed for the bio-assay of a specific growth factor, which is included in low, but adequate concentration; the addition of the agent to be tested can disturb growth only by competing with that specific factor.

Tissue culture screening methods use normal and malignant human and animal cells growing in tissue culture. The addition of a cytotoxic agent induces morphological and growth changes in the cells which can be seen on direct microscopy. While non-malignant cells can hardly be regarded as normal when growing in culture, it is important to note that most of the anti-tumour agents are highly and unselectively cytotoxic against normal and malignant cells *in vitro*. It may be inferred that the apparently selective anti-tumour activity shown by some of these compounds *in vivo* is due to host-imposed differences that do not obtain in tissue culture.

At the same time, Wright *et alii* (1957) have shown a fairly close measure of positive correlation between the effect in tissue culture of an agent on a particular human tumour, and the clinical response of that same tumour to that agent. In Wright's clinic biopsy material from tumour areas is grown in tissue culture, and then tested against a range of cytotoxic drugs *in vitro*. Whenever possible, this information is used to decide which drugs are likely to return clinical dividends. Clinical and tissue culture responses of the particular tumour to each drug are compared. Their results highlight the differences in response between primary cell cultures of established cell lines (Cobb and Walker, 1958) and the differences in response according to patient source rather than pathological cell type.

A variation of this technique used by Boyes *et alii* (1960) analyses by paper chromatography the uptake by the incubated tumour cells from the culture medium of various amino-acids. The influence of chemotherapeutic agents and hormones is assessed by their effect on this absorption. The absorption pattern indicates the tumour's metabolic needs and areas of sensitivity, and blocking of absorption indicates the agent's ability to interfere.

Animal tumour screening methods utilize spontaneous and transplantable tumours, especially in pure lines of mice and rats. The compound under trial is introduced in varying doses by diverse routes. The success of the agent is measured in terms of tumour regression (which is frequently complete), reduction in number and size of metastases, and prolongation of expected life.

Human tumours in heterologous hosts have been used to permit *in-vivo* testing which would approximate to the conditions in the original host. Transplantable human tumours are grown in rats and mice with the help of X-irradiation and cortisone to inhibit immunological rejection, in hamsters with the aid of cortisone alone and in eggs and tissue culture without adjuvant treatment (Handler *et alii*, 1959; Toolan 1957, 1958).

Testing of agents against these tumours can provide screening information or it can be used to assess the probable responsiveness of a particular human tumour to various agents after the transplantation of a biopsy specimen—for example, to hamster cheek pouch (Adams, 1959).

Southam (1949) has used human homotransplantation of tumours (which grow up to four weeks in patients with advanced cancer) and tested chemotherapeutic agents against them *in vivo*.

A combined method for "tissue culture *in vivo*" is the implantation of tumour in a diffusion chamber introduced into a skin fold of an animal (Algire, 1956). The diffusion chamber separates this heterologous tissue from the host, and the immune response is not initiated. To date, the technique has been most useful, not in screening, but in separating direct necrotizing effects of agents on cells from hæmorrhage and necrosis due to capillary stasis in the small vessels supplying the tumour, such as occurs with bacterial polysaccharides and podophyllin (Algire *et alii*, 1954).

Probabilities and Possibilities.

The future is impossible to predict in a completely empirical field. Certainly there will be the intermittent drama of a new "break through", but until more useful principles can be established to form a basis of logical investigation, progress must be haphazard.

The problem differs from that of antibacterial therapy, where the body is assisted in its disposal of living cells, as well as dead and dying cells. Many attempts have been made to establish and exploit immunological dif-

ferences between normal and neoplastic cells to encourage the body to scavenge its own parasite. A single real difference here would produce many opportunities.

Clearly the problem turns on the metabolic differences of a malignant cell from the normal, so that some qualitative difference can be exploited quantitatively. This is to over-simplify the problem. We know little enough of the differing metabolisms between adjacent normal cells, and we can be sure that the differing properties between various malignant tumours reflect different metabolisms, let alone the variations of the stem cell of a particular cancer from its progeny. So far the investigations of the properties of cancer cells show more similarities than differences when compared with their inhibited normal counterparts.

In other words, cancer chemotherapy is at the wrong end of the problem, pushing blindly to find a solution to a problem when there is not yet evidence that a solution is possible. In another decade or so, cancer chemotherapy may well be appropriate, when the directions in which it is worth looking have narrowed.

A more logical programme derives from the mutation hypothesis of malignant disease in which the deletion or addition of genetic material (deoxyribonucleic acid, DNA) begins a family of delinquent cells. Where purine and pyrimidine antagonists act as antimetabolites for the synthesis of precursors of nucleic acids, more specific disruption of cells may be achieved with substituted nucleotides whose incorporation into DNA will impair its ability to replicate; or if the uninhibited division of tumour cells results from the absence of a feed-back system of control (Potter, 1957), the provision of this system, theoretically at the level of the RNA enzyme forming systems, will restore cellular behaviour to normal. Much more information on nucleic acid chemistry is necessary before such elegant approaches are feasible. Perhaps we can cultivate a series of viruses with appropriate DNA constituents which will selectively swarm on neoplastic cells after the manner of virus bacteriophages.

SUMMARY.

An outline has been given of the beginnings of the work in cancer chemotherapy. The basic information on the "staple" drugs has been summarized.

Some of the directions and methods of present investigations are indicated.

REFERENCES.

A complete list of references is available on request to the writer of this article.

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Books Received.

[The mention of a book in this column does not imply that no review will appear in a subsequent issue.]

"A Short History of Clinical Pathology", by W. D. Foster, M.D. Cantab., with a chapter on "The Organisation of Clinical Pathology to the Present Day", by S. C. Dyke, D.M., F.R.C.P.; 1961. Edinburgh, London: E. & S. Livingstone Ltd. 8¾" × 6¼", pp. 154, with illustrations. Price: 27s. 6d. (English).

"Hypertension—Chemical and Hormonal Factors. Volume IX: Proceedings of the Council for High Blood Pressure Research, American Heart Association, November, 1960", edited by F. R. Skelton, M.D., Ph.D.; 1961. New York: American Heart Association, Inc. 11" × 8", pp. 95, with illustrations. Price: $2.50.

"Feinstruktur einer Allgemeinpraxis: Diagnostische und statistische Ergebnisse", by Robert N. Braun, with a foreword by Univ.-Prof. Dr. Hans Schulten; 1961. Stuttgart: Friedrich-Karl Schattauer-Verlag. 9¼" × 6¼", pp. 136. Price: DM 24.50.

"The Extra Pharmacopœia (Martindale): Supplement 1961 to Volume II Twenty-Third Edition 1955 and Volume I Twenty-Fourth Edition 1958", by the Council of The Pharmaceutical Society of Great Britain; 1961. London: The Pharmaceutical Press. 7¼" × 4¼", pp. 316. Price: 32s. 6d.

"The Penguin Handbook of First Aid and Home Nursing", by A. C. White Knox and J. E. F. Gueritz, with illustrations by Andrea Breese; 1961. Middlesex, Baltimore, Victoria: Penguin Books Pty. Ltd. 7¼" × 4¼", pp. 28. Price: 5s. 6d.

"Good Health in the Tropics: Advice to Travellers and Settlers", by W. H. Jopling, M.R.C.P. (Lond.), M.R.C.P. (Edin.), D.T.M. & H. (Eng.); 1961. Bristol: John Wright & Sons. 6" × 4", pp. 32. Price: 3s. 6d.

"Biochemists' Handbook Compiled by One Hundred and Seventy-One Contributors", edited by Cyril Long, M.A., B.Sc., D.Phil., F.R.S.E.; 1961. London: E. & F. N. Spon Ltd. 9¾" × 6", pp. 1192, with illustrations Price: 168s.

"Fifty-Fifty: Questions and Answers on Your Life", by E. P. Blamires; 1961. Christchurch: Whitcombe & Tombs Ltd. 8½" × 5½", pp. 86. Price: 12s. 6d.

"Starling's Law of the Heart: Its Significance in Chronic Congestive Heart Failure", by Loe Ping Kian, M.D.; 1961. Djakarta: Keng Po. 9½" × 6½", pp. 88. Price: Harga Rp. 95.

"Hypokinetic Disease: Diseases Produced by Lack of Exercise", by Hans Kraus, M.D., and Wilhelm Raab, M.D., with a foreword by Paul D. White, M.D.; 1961. Springfield: Charles C. Thomas; Oxford: Blackwell Scientific Publications. 9" × 6", pp. 104, with illustrations. Price: 60s. (English).

"Genetics and Ophthalmology", by P. J. Waardenburg, M.D., A. Franceschetti, M.D., and D. Klein, M.D.; 1961. Oxford: Blackwell Scientific Publications Ltd.; Assen: Royal Van Gorcum; Springfield: Charles C. Thomas. 10" × 7", pp. 992, with many illustrations. Price: £13 10s.

"Illustrations of the Nervous System: Atlas III", by Louis Hausman, M.D.; 1961. Springfield: Charles C. Thomas; Oxford: Blackwell Scientific Publications. 11" × 8½", pp. 168, with many illustrations. Price: 76s.

"Selected Readings in Pathology", by Esmond R. Long, M.D., Ph.D.; Second Edition; 1961. Springfield: Charles C. Thomas; Oxford: Blackwell Scientific Publications. 9½" × 6¼", pp. 306, with illustrations. Price: 68s.

"The Spinal Cord: Basic Aspects and Surgical Considerations", by George Austin; 1961. Springfield: Charles C. Thomas; Oxford: Blackwell Scientific Publications. 10" × 7", pp. 532, with many illustrations. Price: £10 12s.

"Chemistry of Digestive Diseases", by John R. Gamble, M.D., and Dwight L. Wilbur, M.D.; 1961. Springfield: Charles C. Thomas; Oxford: Blackwell Scientific Publications. 9" × 6", pp. 120. Price: 36s.

"Health in Industry: A Guide for Engineers, Executives, and Doctors", by R. C. Browne, M.A., D.M. (Oxon.), M.R.C.P. (London); 1961. London: Edward Arnold (Publishers) Ltd. 8¾" × 5¼", pp. 158, with illustrations. Price: 18s. net (English).

"Radioactivity in Man: Whole Body Counting and Effects of Internal Gamma Ray-Emitting Radioisotopes"; A Symposium held at the Vanderbilt University School of Medicine, edited by George R. Meneely, M.D.; 1961. Springfield: Charles C. Thomas; Oxford: Blackwell Scientific Publications. 9" × 6", pp. 492, with illustrations. Price: £6 12s.

"Cancer of the Nasopharynx: Its Natural History and Treatment", by M. Lederman, M.B., D.M.R., F.F.R.; 1961. Springfield: Charles C. Thomas; Oxford: Blackwell Scientific Publications. 9" × 6", pp. 117, with illustrations. Price: 54s.

Annals of the New York Academy of Sciences, Volume 92, Art 3: "Pavlovian Conference on Higher Nervous Activity", edited by Nathan S. Kline; 1961. New York: The Academy. 9" × 6", pp. 813-1198, with illustrations. Price: not stated.

"Penguin Science Survey 1961, Part I: Astronomy, Chemistry, Electronics, Geophysics, Meteorology, Physics, Space Research", edited by Arthur Garratt; 1961. 7¼" × 4¼", pp. 240, with illustrations. Price: 8s. 6d.

"Penguin Science Survey 1961, Part 2: Biology, Genetics, Agriculture, Medicine, Zoology", edited by S. A. Barnett and Anne McLaren; 1961. 7¼" × 4¼", pp. 252, with illustrations. Price: 8s. 6d.

"Physiology for Nurses", by Deryck Taverner, M.B.E., M.D., F.R.C.P.; with illustrations by H. Grayshon Lumby, M.S.I.A.; 1961. London: The English Universities Press Ltd. 8½" × 5½", pp. 236, with illustrations. Price: 23s. 6d.

"Neuro-Psychopharmacology", Volume 2; Proceedings of the Second Meeting of the Collegium Internationale Neuro-Psychopharmacologicum, edited by E. Rothlin; 1961. Amsterdam, London, New York, Princeton: Elsevier Publishing Company; London: D. Van Nostrand Company Ltd. 9¼" × 6¾", pp. 522. Price: 120s. (English).

[1] This review was prepared during the tenure of a grant from the Anti-Cancer Council of Victoria.

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THE SHAPING OF A NEW ASSOCIATION.

On a number of occasions recently the suggestion has been made, with palpable sincerity, that the moves for the formation of the Australian Medical Association have proceeded with undue haste and without sufficient opportunity for discussion by interested members of the British Medical Association in Australia. In the hope that it may help to clear the air and with no wish to arouse controversy we thought it might be as well to set out for present and future reference the history of the matter as it is recorded.

When the Federal Council met in Sydney in March, 1959, it noted[1] a letter which had been sent by the executive officers of the Council to the Branches in February, 1959. In this they (the executive officers) had pointed out that they were fully aware of the fact that there was an increasing number of members who said that the profession in Australia should have its own Australian Medical Association, independent of, but affiliated with, the British Medical Association. Moreover, the executive officers were of the opinion that this would inevitably take place. However, they were firmly of the opinion that it would not redound to the credit of the profession in Australia if the reason for breaking away from the parent body was an increase in the overseas rate of subscription—a subject then very much under discussion, and the primary subject of the executive officers' letter. This proposed increase undoubtedly brought the idea of an Australian association into focus in some people's minds, but it cannot fairly be regarded as having given rise to the idea, which had been slowly taking shape for a considerable time. The Federal Council therefore endorsed the executive officers' appeal to the Branches that they should agree to the proposal of the parent body to increase the subscription rate, and at the same time it resolved to take the necessary steps to investigate the possibility of formation of a medical association of Australia, realizing of course that the matter was necessarily one for the individual State Branches. We highlighted the Federal Council's decision in a leading article at the time.[2] This, it should be noted, was well over two years ago, and two months earlier we had referred to the same matter of an Australian association, also in a leading article.[3] The fact that no subsequent letters of protest appeared in our correspondence columns, which are an open forum, might at least be interpreted to indicate lack of strong opposition to the idea.

At the next meeting of the Federal Council[4] (in September, 1959) a resolution was passed expressing the opinion that the time was now opportune to proceed with the formation of an Australian Medical Association, this opinion to be forwarded to the Branches with the request that the views of members be obtained. Realizing the difficult and tedious nature of the task of devising the constitution and machinery of such an association, the Federal Council empowered its executive officers to formulate detailed proposals on these matters for presentation at the Council's next meeting. This action was taken in the light of personal contact that had been made in England by the President of the Federal Council with officers of the parent body, the results of discussions of the subject by Branch Councils and a statement on the pros and cons of the development prepared by the General Secretary of the Federal Council. All these points were set out in detail in the report of the Federal Council and in a leading article[5] published in the same issue. Still there was no evidence that any member of the profession at large wished to protest or comment.

The matter was then dealt with by the several Branches according to the particular machinery existing in each Branch, and the results were reported to the Federal Council at its meeting in February, 1960.[6] In New South Wales there had been general approval from local associations and from special groups with only minor amendments, and the Branch Council expressed approval. In Victoria a resolution of approval had been passed by Branch Convocation, and the Branch Council had subsequently approved Convocation's resolution. In Queensland circulars had been sent to 1341 members, of whom 332 had replied; 309 had agreed with the suggestion, 15 had disagreed, 2 were undecided, and the replies of 6 were informal. In South Australia there had been general approval from the local associations, the metropolitan groups and the specialist groups; the Council had made a number of constructive and detailed suggestions relating to the name and constitution of the new association. In Western Australia there had been approval, but it was suggested that the name be the Medical Association of Australia. In Tasmania there had been general approval of the Federal Council's resolution as such. The Federal Council then discussed the constitution of the proposed new association, including a consideration of the possible relationship to it of the Colleges and other associations of medical practitioners in Australia. The upshot of this was the appointment of the steering committee, which has since then done a great deal of hard work on the matter. Its brief was to consider ways and means of forming an Australian Medical Association, to consult the Association's legal advisers and

[1] Med. J. Aust., 1959, 1: 681 (May 16).
[2] *Ibid.*, 1959, 1: 672 (May 16).
[3] *Ibid.*, 1959, 1: 404 (March 21).
[4] *Ibid.*, 1959, 2: 734 (November 14).
[5] *Ibid.*, 1959, 2: 727 (November 14).
[6] *Ibid.*, 1960, 1: 508 (March 26).

to produce a draft constitution for submission to the Federal Council. Again the matter was given additional publicity in a leading article,[7] as we were concerned that the profession should be kept informed on these developments and that it should be encouraged to interest itself in them. We then pointed out that this was the vital stage of the matter and expressed the hope that it would receive the fullest discussion in the columns of the Journal and elsewhere. A letter from the Chairman of Council of the Parent Body, extending good wishes for the new association, and the reply of the President of the Federal Council to it were published in our editorial columns[8] about three months after the Federal Council meeting. Apart from a couple of passing references, which were not critical of the Federal Council's proposals, our correspondents still maintained the silence which is usually accepted as indicating approval.

By the time of the Federal Council's next meeting[9] (in August, 1960) a draft constitution had been prepared and submitted to the Branches for their consideration and comment, and the proposals from the previous meeting had been communicated to interested bodies both within and outside the B.M.A. In the light of the Branches' views the Federal Council dealt with the draft in detail and set in motion the machinery for a convention of interested bodies to consider the draft as amended. Again we drew attention in these columns[10] to what had taken place, emphasizing that on the one hand the draft constitution needed to be "thoroughly kicked around" at that stage rather than later and on the other that it was probably not humanly possible to please everyone, but the Federal Council was determined to try its hardest to do so. At this stage evidence of wider interest began to be shown. Considerable discussion went on in the Branches. We published a number of thoughtful letters, including some from leading members of the profession, and the convention at the end of November, 1960, had a large and representative attendance which expressed itself well and to the point. The convention was reported in full and editorial comment was made which we need not repeat.[11] It is enough to say that the draft constitution was approved with some recommended modifications. There was widespread disappointment that it had not proved possible to bring in such bodies as the Royal Colleges, but the difficulties in the way were unquestionably valid. At least the air had been to some extent cleared. The Federal Council met immediately after the convention, and referred the draft constitution with the recommendations of the convention back to the steering committee. It was then possible to present to the Federal Council at its next meeting[12] (in March, 1961) a draft of the constitution in the more appropriate form of Memorandum and Articles of Association. This after consideration was referred to the Branches, where it appears to have received particularly critical examination, and the Branches' views were brought forward at a special meeting of the Federal Council in June, 1961. In the meantime the idea of submitting the draft constitution to a referendum of members of the B.M.A. in Australia had been strongly canvassed in our correspondence columns, notably by the President of the Queensland Branch[13] and by a former President of the Federal Council, Sir Henry Newland.[14] Replying to this suggestion the President of the Federal Council, Dr. H. C. Colville, set out reasons why he considered it impracticable. At the special meeting of the Federal Council,[15] which was of course the critical one, four Branches expressed their readiness to go ahead with the new Association in terms of the draft Memorandum and Articles of Association, but the Queensland and Western Australian Branches were reluctant to do so, asking that further consideration be given to difficulties in the constitution, notably those associated with the Federal Assembly. This would necessarily have further delayed the progress of formation of the new Association, and the Federal Council as a whole was unwilling to do this. The draft constitution was approved and adopted, and the executive officers were authorized to bring the matter to finality. Subsequently the Queensland and Western Australian Branches signified their willingness to take their place in the new Association while, quite properly, reserving their right to maintain their criticism of details of the constitution.

This somewhat tedious recital of the events of the past two and a half years will, we hope, put the matter in perspective. It is our wish, as we have said, not to arouse controversy, but rather to make it clear that the Federal Council has not acted precipitately or in any hole-in-the-corner fashion. Every step has been referred to the several Branches in accordance with the Federal Council's normal method of working, and the Branches have been responsible for ascertaining the views of their members in their several, quite diverse ways. It is only fair that the Federal Council of the B.M.A. in Australia, which is holding its last meeting in Brisbane this weekend, should be recognized as having acted in good faith throughout, and that the members of the Steering Committee should be credited with having done a difficult job well. The history of the matter surely shows that the new Association, when it emerges officially on January 1, 1962, will have been brought into being with no more than reasonable expedition.

[7] *Ibid.*, 1960, 1: 501 (March 26).
[8] *Ibid.*, 1960, 1: 817 (May 21).
[9] *Ibid.*, 1960, 2: 390 (September 3).
[10] *Ibid.*, 1960, 2: 385 (September 3).
[11] *Ibid.*, 1960, 2: 986, 981 (December 17).
[12] *Ibid.*, 1961, 1: 564 (April 15).
[13] *Ibid.*, 1961, 1: 758 (May 20).
[14] *Ibid.*, 1961, 1: 877 (June 10).
[15] *Ibid.*, 1961, 2: 70 (July 8).

Comments and Abstracts.

NEPHROCALCINOSIS.

ACCORDING to L. N. Pyrah and A. Hodgkinson,[1] the term "nephrocalcinosis" was first used by F. Albright and A. B. Reifenstein in 1948 to describe the diffuse renal parenchymal calcification seen occasionally in association with hyperparathyroidism. Since then it has become established as primarily a radiographic diagnosis, and is used to describe the same appearance in a diverse group of unrelated conditions. It is therefore not to be regarded as a clinical entity, but as a purely descriptive term, used in any condition which gives rise to this

[1] *Brit. J. Urol.*, 1960, 32: 361 (December).

appearance. Pyrah and Hodgkinson state that microscopic calcific foci, which are not discernible radiologically, may be demonstrated in most, if not all, kidneys whether normal or pathological, but that these deposits tend to be more numerous and more pronounced in a variety of conditions—for example, acute alkalosis resulting from pyloric stenosis from any cause, multiple myelomatosis, hypervitaminosis D, and Fanconi's syndrome. There is a further group of conditions in which renal parenchymal calcification progresses to a point where it is demonstrable radiographically, when the aggregates of calcium salts are of at least pinhead size. It is this group to which Pyrah and Hodgkinson consider the term nephrocalcinosis should be applied. Such calcific foci often appear in the collecting tubules of the renal papillæ, whence they may emerge as small calyceal stones; these may produce clinical symptoms such as pain and hæmaturia, and may be passed spontaneously down the ureter. Since nephrocalcinosis is primarily a radiographic diagnosis, the surgeon has to be careful not to include in this term unusual examples of renal calculosis, such as the multiple diffuse, laminar calculi seen occasionally in pyonephrosis, the diffusely distributed recumbency calculi of spinal injury, or the dystrophic calcification of renal tuberculosis.

Pyrah and Hodgkinson analyse a series of 76 cases of nephrocalcinosis seen over the last few years. Twenty-four of these are from their own clinic, and the remainder were collected from members of the British Association of Urological Surgeons. The disease was nearly always bilateral and occurred at all ages (5 to 62 years in this series). In 32 of the 76 cases, true parenchymal nephrocalcinosis was associated with calculi in the main urinary passages (from calyces to bladder). In the majority of cases urinary tract symptoms were present, but a few patients showed no such symptoms. Since nephrocalcinosis may be the expression of a non-renal disease, a full general examination must be made, and this should include any irregularity or abnormality of the diet, especially excessive intake of vitamin D, milk, alkalis or sulphonamides. The commonest radiographic appearance is of spotty calcific debris or tiny stones in the pyramids of both kidneys. True calyceal calculi may also be present.

The only comparable series of which Pyrah and Hodgkinson are aware is one comprising 91 cases, 43 of them from the Mayo Clinic, published by J. D. Mortensen and J. L. Emmett[2] in 1954, and they compare the findings. In Mortensen and Emmett's series hyperparathyroidism was the underlying cause of the condition in 41% of cases, but in their own series it was responsible for only 11 cases (about 16%).

Pyrah and Hodgkinson state that true nephrocalcinosis is much less common than ordinary calculus formation as the renal expression of hyperparathyroidism. About one-fifth of the cases occurred as a sequel of primary renal acidosis. This may be associated with hypokalæmia; treatment in these cases is by the administration of Shol's solution (citric acid, citrates and water) for an indefinite period. Urinary infection was present in 11 cases, but in only three was this listed as the primary cause. Other causes were: the milk-alkali syndrome, arising from excessive ingestion of these substances (two cases); oxalate nephrocalcinosis (two cases); medullary sponge-kidney, first described by G. Lenarduzzi in 1939, in which the medulla presents a cystic or spongy appearance and tiny stones form in these areas (one case was proved, but in 13 others a very tentative diagnosis of medullary sponge kidney was made, though further study was needed to establish this). No cases of nephrocalcinosis associated with renal sarcoidosis or with chronic glomerulo-nephritis occurred in this series, though these have been described by other authors. Nearly one-third of the series had to be classed as idiopathic; in these the blood chemistry was normal, there was no infection and radiographic contrast studies showed fairly normal appearances. Moreover, there was no obvious generalized disease. Possibly these cases are the result of some as yet unknown biochemical abnormality, or the end result of a past infection. Many of these patients do not suffer attacks of pain or deterioration in their health.

[2] *J. Urol.* (*Baltimore*), 1954, 71: 398 (April).

RESULTS OF FLUORIDATION IN HASTINGS, NEW ZEALAND.

SIX AND A HALF years' experience of fluoridation in the city of Hastings, New Zealand, has shown that children who have been drinking fluoridated water all their lives have a reduction of 74% in dental decay, a possible world record in the reduction of dental decay resulting from the use of fluoridated public water supplies. World Health Organization representatives attending the twelfth session of the Western Pacific Regional Committee meeting in Wellington, New Zealand, were told this by Colonel J. Ferris Fuller, Director of Dental Services for the New Zealand Armed Forces, and leader of the committee's technical discussion on dental health. Colonel Fuller said that, so far as he knew, the results in Hastings from the use of fluoridated water in preventing dental disease were the best in the world to date. Commenting on further results from the fluoridation in Hastings, he said that whereas 24·4 permanent teeth per 100 were decayed, missing or filled in 1954, only 6·3 were now affected. Seven-year-old children who had benefited from fluoridated water for most of their lives had a reduction of 50% and eight-year-olds had a reduction of 48%. Children aged nine years, whose teeth were already calcified when fluoridation began, had a reduction of 32%. As far as children completely free from dental decay were concerned, there was among five-year-olds a fivefold increase. The same increase applied also to six-year-olds. Among seven-year-olds there was an eightfold increase in immune children. Colonel Fuller said that dental decay had been such a problem in New Zealand, one that touched every household, that the public had almost resigned themselves to the belief that it was their lot. It was startling, therefore, to see the reductions quoted taking place before their eyes and to realize that it could actually happen.

Colonel Fuller went on to say that workers in the public-health field the world over had accepted fluoridation as an established public-health measure long past any experimental stage, doing no harm to anyone but great good to many. It had been accepted by the World Health Organization, and dental and medical associations the world over had endorsed it. Fluoridation demonstrated man's control through science of yet another preventable disease that had been a source of pain and ill health through the ages. However, something else had been demonstrated as well, and Colonel Fuller commented significantly: "In the highly developed countries where the democratic processes have full play, it is difficult to persuade a community to adopt a measure such as this, even though it is to the ultimate benefit of themselves and future generations. The reasons for this are another story. In the final analysis, the decision rests with the elected representatives of the people who are in office to make decisions on matters such as this after taking competent advice on the subject. Many elected representatives with a fear of the ballot box shirk this responsibility."

THE CHILD FOR WHOM NOBODY LOOKED.

RECENTLY in Ontario a study was made by M. W. Partington[1] of children known to be suffering from phenylketonuria in that State. The material was drawn from three main sources—the Hospital for Sick Children, the Ontario Hospital Schools and individual patients receiving private treatment. The number studied was 83. The population of Ontario was just over 6 million in 1960 and on

[1] *Canad. med. Ass. J.*, 1961, 84: 985 (May 6).

the basis of previous surveys elsewhere, which agree fairly well that the incidence of the disease in populations of predominantly European descent is about one in 25,000 persons, Partington estimates that the total number of phenylketonuria sufferers in Ontario is approximately 240. That is, about 160 sufferers from phenylketonuria were not included in the survey. He speculates as to where they might be found. He suggests that a search among retarded children attending private practitioners or pædiatric hospitals, and in other schools for retarded children, might produce a reasonable yield, but is of the opinion that an unknown number of undetected sufferers are living their lives out under a burden of mental defectiveness—a burden which could today be lifted by early detection and treatment of the disease.

The fact that the detection of phenylketonuria is such a simple matter, and the treatment, if employed early enough, so successful makes it a needless tragedy that children's lives should be thus blighted. The critical period for the detection of the disease and the institution of treatment is in the first few weeks of life, when prompt action will result in a child growing up with intelligence within the normal range. The relative infrequency of the disease is no argument against a vigorous attempt to meet its challenge. We discussed this question fairly fully in a recent leading article,[2] but it is prehaps worth repeating that the expense to the community of mass screening of infants would be infinitely less than the years-long custodial care of unmanageable, often destructive "imbeciles", apart from the wastage of human potentialities. The detection of the disease involves no more than the testing with "Phenistix" of a freshly wet napkin. Unfortunately routine screening of infants in maternity hospitals is useless since the phenyl compounds do not appear in the urine until about the third week of life. However, routine testing of the infant's urine when the mother returns for her post-natal check, or at the child's first visit to the baby health centre, should identify most cases. This is already being done in several States in Australia, and will probably soon be universal practice. For various reasons including the fact that not all children are brought to health centres, some phenylketonurics will escape this net. Phenylketonuria should therefore be kept in mind whenever associated conditions are encountered. Partington stresses the high incidence of infantile eczema among phenylketonurics, but the first indication that something is wrong may present as a simple feeding problem. The necessity of identifying the disease before frank mental defect becomes apparent cannot be overstressed. The earlier the detection the more chance of success, and nothing can recall the lost years of opportunity for the child for whom nobody looked.

SHORTER ABSTRACTS.

UROLOGY.

RENAL PAPILLARY NECROSIS. A. B. Rutner and D. R. Smith, *J. Urol.* (*Baltimore*), 1961, 85: 462-470 (April).

THE authors report four cases of renal papillary necrosis which they describe as an uncommon lesion of undetermined cause. It is nearly always associated with urinary tract infection, and often occurs in the presence of diabetes mellitus, obstructive uropathy and chronic interstitial nephritis with phenacetin abuse. The clinical categories are, roughly, acute, subacute and chronic. There is a coagulative necrosis of one or more renal papilla, and patients may pass this tissue in the urine. It is to be suspected in patients who have an acute exacerbation of a chronic infection of the urinary tracts; in diabetics in coma, who also have pyelonephritis and progressive azotæmia; in patients with an obstructive uropathy who suddenly develop a fulminating infection. Characteristic radiological signs are visible when urographic delineation is clear. In the papillary form, haziness of the normally sharp calyceal cup is noted early in excretion urograms. As necrosis develops and sequestration begins, the medium penetrates around the area of necrosis forming "sinus tracts", later "arc shadows", and finally "ring shadows". With absorption or extrusion of the sequestrum, the calyx appears club-shaped. Extruded papillæ may lodge in the pelvis or ureter and appear as filling defects. In the medullary form of the disease, the urograms remain normal until the medium penetrates the papilla and gets into the area of necrosis, forming "sinus tracts". Extrusion of necrotic material results in an irregular medullary cavity. When this disease is suspected, vigorous antibiotic therapy should be started, diabetes brought under strict control and any urinary tract obstruction alleviated. Because of the frequency of bilateral lesions, vigorous conservative measures are indicated in most cases. Death often follows, but, with improvements in early diagnosis, the survival rate has been increasing.

TUMOURS OF THE SPERMATIC CORD. W. Dreyfuss and E. Goodsitt, *J. Urol.* (*Baltimore*), 1960, 84: (November).

FOUR cases of malignant tumour of the spermatic cord are reported. All the tumours were sarcomas (one fibrosarcoma, one myxosarcoma, one leiomyosarcoma, one liposarcoma). In the last case the diagnosis of simple lipoma was considered, and it was in fact the least active tumour of the four. In three cases trauma drew attention to the presence of the tumour, sometimes by causing hæmorrhage, necrosis and pain. The authors point out that it is possible that some tumours of this type could arise in the retroperitoneal portion of the cord between the origin of the vas and its entrance into the inguinal canal, but state that no such case has yet been published. Early diagnosis is difficult and all the tumours in this series were extensive. Local removal of the tumour, together with the contents of the scrotum, is indicated. Whether it is mandatory to do a block dissection of all draining lymph glands, or to irradiate them, is not certain, though in some cases autopsy has shown widespread lymph-node involvement. However, the authors comment that, being sarcomas, these tumours would tend to metastasize through the blood stream.

PENETRATING RENAL WOUNDS. R. Scott, jun., *J. Urol.* (*Baltimore*), 1960, 84: (November).

THE author presents an analysis of 100 penetrating renal injuries. In 20% of these cases hæmaturia did not occur; therefore the absence of blood in the urine should not make one too confident in ruling out renal injury. Excretion urography was of diagnostic value in 64% of these cases. The author thinks that this examination should be performed in all cases of penetrating abdominal injuries if the patient's condition permits, not only to define the extent of possible renal injury but also to establish the functional capacity of the opposite kidney. The incidence of complications following non-surgical treatment of penetrating renal injury in this series was 17%. The combined incidence of complications after all forms of surgical treatment of these injuries was only 5%. The author therefore suggests that when renal injury is determined the kidney should be explored. In 80% of these cases associated injuries of intraperitoneal structure were found; therefore an exploratory laparotomy is indicated in all cases. The author states that the performance of excretion urograms should be delayed for several hours until primary shock has disappeared; otherwise contraction is so poor because of low blood pressure that films are useless. When the threat of exsanguination is a very serious one, immediate operation should take priority.

ISOLATED RECTUM FOR URINARY DIVERSION. J. W. Dorsey and R. W. Barnes, *J. Urol.* (*Baltimore*), 1961, 85: 569-572 (April).

THE authors state that upper urinary tract dilatation and hyperchloræmic acidosis have been the chief disadvantages of the much-used uretero-sigmoidoscopy. These late complications can be largely eliminated by isolating the rectal segment of the bowel so that it can act as a safe urinary reservoir. This report is based on a combined series of 25 cases, carried out by the authors, working independently of each other. The ideal method of urinary diversion should incorporate the following objectives: (i) sphincter control of both urine and fæces; (ii) freedom from recurrent pyelonephritis and electrolyte imbalance; (iii) social and psychological acceptability; (iv) efficient, uncomplicated surgical techniques. Diversion of the urine through the isolated rectal segment, combined with a permanent abdominal colostomy, separates urine and fæces; it provides voluntary control of the urine, and partial

[2] Editorial, MED. J. AUST., 1961, 2: 361 (August 26).

control of semi-solid fæces. A more advanced method (used in 9 of the 25 cases in this series) is to make the colostomy also in the perineum by pulling the sigmoid segment down and then through (and inside) the external rectal sphincter. In the series of 16 with an abdominal colostomy, the ages of patients ranged from the fourth to the seventh decades. Thirteen had carcinoma of the bladder. Of this latter group, four are living at three, five, six and eight years after operation respectively. The remainder have succumbed to metastases. All patients with benign lesions are living and well. Of the nine patients in whom a perineal colostomy was made, five were children with congenital anomalies. Of the four adults, three had carcinoma of the bladder and the other a tuberculous contraction. The longest follow-up is four years, but so far there has been no death in this series, although there have been troubles such as wound dehiscence, fæcal soiling, leakage of urine and contraction of the stoma. The authors conclude with the caution that they do not wish to convey the impression that with this procedure biochemical changes do not occur at all. There is some reabsorption of urea through the rectum. Serum potassium remains at a low-normal level for many months, but there is no evidence of large potassium loss. Slight hyperchloræmic acidosis has been recorded.

DERMATOLOGY.

BENIGN HYPERGLOBULINÆMIC PURPURA. R. W. Goltz and R. H. Good, *Arch. Derm.*, 1961, 83: 26-38 (January).

THE authors discuss the relationship of benign hyperglobulinæmic purpura to Mikulicz's disease, the sicca syndrome of Gougerot and Sjögren and epidermolysis bullosa dystrophica. They consider that there is strong evidence that these are closely related, if not identical diseases; varying only in their most permanent clinical manifestations. Five cases are reported. Two of these demonstrate hyperglobulinæmic purpura and Mikulicz's disease. Two other patients are brothers with epidermolysis bullosa dystrophia. Both brothers have hyperglobulinæmia, but as yet only one has developed spontaneous episodes of purpura. The fifth patient presented because of unusual, papular pernio lesions, occurring in association with hyperglobulinæmia. Histologically the three patients with hyperglobulinæmic purpura show a characteristic angiitis in the dermis and hypodermis. This angiitis is similar, if not identical, to that observed in rheumatoid and hypersensitivity states and certain other cutaneous diseases. It is postulated that the hyperglobulinæmia and angiitis may not be casually related, but rather that both processes may be the result of the same fundamental disturbance. Finally, brief consideration is given to the resemblance between purpura associated with hyperglobulinæmia and other purpuric and hæmosideric diseases.

SOME UNUSUAL ALLERGIC REACTIONS IN INDUSTRY. M. M. Key, *Arch. Derm.*, 1961, 83: 3-6 (January).

IN a discussion of some unusual allergic reactions in industry, it is pointed out that these can take many forms. The most common form is allergic contact dermatitis, which accounts for about 20% of contact dermatitis in industry. Less common is occupational asthma, which may be associated with contact dermatitis. Examples of asthma-dermatitis exposures are metal dusts and compounds, castor bean pomace, toluene diisocyanate, spices, flour and wood dust. Occupational urticaria is rare, but has been caused by inhalation of aliphatic polyamines, castor bean pomace, sulphur dioxide, ammonia and formaldehyde.

NEW THERAPEUTIC AGENT FOR TINEA VERSICOLOR. E. H. Zimmerman, *J. Amer. med. Ass.*, 1961, 176: 23 (April 8).

THE author states that the diagnosis of tinea versicolor presents no problem, but that its treatment in the past has been unsatisfactory. Recurrences were frequent despite prolonged daily applications of the medications available. The newer fungicidal preparations containing undecylenic acid and/or its salts have proved entirely ineffective against the infecting fungus, *Malassezia furfur*. The same is true of oral treatment with griseofulvin, which may even cause an exacerbation of the condition. The author presents the results of a preliminary trial of a new compound, 9-aminoacridinium 4-hexylresorcinolate, in a series of 40 patients with this infection. In 32 patients, complete clearing occurred after a single course of treatment lasting four to eight weeks; in seven others this was achieved after a second similar course. No signs of primary irritation or allergic sensitization were observed in any case. The drug was applied in one of three forms, as a lotion containing 2 mg. per ml. in propylene glycol, as a cream containing 2 mg. per gramme in a water-washable base, and as an aerosol spray. All appeared to be equally effective, and were well accepted by the patients. The medication was applied each evening after bathing, without scrubbing. It was also tried on 26 other patients suffering from various other common dermatophytoses, but the results in these patients were consistently poor. The authors conclude that 9-aminoacridinium 4-hexylresorcinolate is almost specific against *M. furfur*, and may prove to be the most effective therapeutic agent for tinea versicolor in the dermatological armamentarium.

TUBEROUS SCLEROSIS. R. C. Duvoirin and W. M. Vinson, *J. Amer. med. Ass.*, 1961, 175: 869-873 (March 11).

THE authors report three cases of tuberous sclerosis without mental impairment. One patient was an epileptic who could be recognized only by pneumoencephalography. The two other patients presented with adenoma sebaceum and intracranial calcification (brain stones). The authors suggest that tuberous sclerosis without mental impairment may be much more common than has previously been thought, and such patients may frequently pass unrecognized.

ACRODERMATITIS ENTEROPATHICA WITHOUT DIARRHEA. B. Portnoy and C. W. Marsden, *Arch. Derm.*, 1961, 83: 420-424 (March).

THE authors report a case of acrodermatitis enteropathica in a child who, at the age of six months, presented with the typical skin lesions, paronychia, alopecia and retarded growth, but in whom no gastro-intestinal disturbance or diarrhœa was seen. This caused some delay in arriving at the correct diagnosis, but when diiodohydroxyquinoline was given in adequate dosage the response was dramatic. A dosage of 200 mg. per day produced no improvement, but some improvement was noted when a dosage of 400 mg. daily was tried, and complete clearance of the lesions was obtained with 600 mg. daily; the patient was eventually stabilized on a dose of 800 mg. daily.

LONG-TERM THERAPY OF ACNE WITH TETRACYCLINE. T. Cornbleet, *Arch. Derm.*, 1961, 83: 414-416 (March).

A GROUP of 38 acne patients, whose condition had failed to show a lasting improvement with shorter term antibiotic therapy, were treated with tetracycline on a long-term basis, and compared with 30 patients treated by topical measures only. Treatment was started with 1000 mg. tetracycline daily and progressively reduced to a maintenance dose which averaged 365 mg. daily. Thirty-six patients were improved or cleared, and this improvement was maintained with continuous treatment for longer than a year. Ten of a group of eleven patients who showed little response to accepted topical therapy improved or cleared with tetracycline. There was no clinical evidence of resistance or tolerance development. The face improved or cleared before the shoulders or back. Relapse often occurred soon after cessation of therapy. Untoward effects were negligible. There was excellent patient cooperation. The author states that this study should be regarded as an investigational one, otherwise effective remedies in addition to that of antibiotics would have been used.

MYCOSIS FUNGOIDES. R. R. Rauschkolb, *Arch. Derm.*, 1961, 83: 217-223 (February).

EXPERIENCE with seven patients who died while under observation in hospital caused the diagnosis of mycosis fungoides to be supplanted by the evolution of the lymphoma as Hodgkin's disease, lymphosarcoma, or monocytic leukæmia in six instances. In one instance, a so-called monocytic leukosis of the skin, there was no lymphomatous involvement of any other organ. Here a final diagnosis of mycosis fungoides may be tenable. Mycosis fungoides is a time-hallowed clinical designation whose integrity has been increasingly jeopardized by the licence of including the *d'emblée* form of Vidal-Brocq and the exfoliative erythroderma of Hallopeau-Besnier, and the obligation of supplanting it with a more precise designation when anatomical diagnosis is available. The author concludes that the very convenience of the term may give the clinician a sense of unwarranted satisfaction in his diagnosis, which might be better left as "lymphoma" whose differentiation he has yet to accomplish.

Medical Societies.

AUSTRALIAN PÆDIATRIC ASSOCIATION: PART II.

THE annual meeting of the Australian Pædiatric Association was held at Canberra on April 21 to 24, 1961, DR. R. H. CRISP, the President, in the chair. Part I of the report of this meeting was published in these columns on October 14, 1961.

Hypothyroidism in Childhood.

DR. H. N. B. WETTENHALL (Melbourne) read a paper entitled "Hypothyroidism in Childhood" (see page 653).

Professor Hubble emphasized that dry thyroid extract was an outmoded drug, and referred to McGregor's recent article.[1] He remarked that skeletal maturation should be watched carefully if top doses of thyroxine were to be used, as Dr. Wettenhall had suggested. He referred to recent work in Birmingham concerned with the ætiology of hypothyroidism. Chenoweth had found antibodies to thyroglobulin in three out of 30 cretins examined, and Fraser had shown a high percentage on non-tasters of P.T.C. in cretins. The latter work suggested that some constitutional predisposition was operating.

DR. FAILING (Sydney) asked the circumstances in which the baby diagnosed in the early neonatal period had been recognized, and what dosage of thyroxine should be employed in neonates.

Dr. Wettenhall was unaware of details of the early history of the baby referred to, but stated that in such young infants he would employ a daily dose of thyroxine of 0·025 mg. initially, increasing the dose until features of toxicity appeared, when a slightly lower dose could be continued for maintenance.

Dr. Kate Campbell mentioned that she had seen a baby born of a mother with hypothyroidism that showed typical features of cretinism at the age of eight days.

Dr. S. J. Robertson referred to two infant cretins who had collapsed within a few hours of initiation of thyroid therapy. He asked Dr. Wettenhall what factors might have been responsible.

Dr. Wettenhall replied that collapse was unusual, and he doubted if it was due to thyroid therapy. Hypothyroidism itself might cause collapse.

Dr. Clair Isbister referred to a woman with Hashimoto's disease, of whose three children two had developed cretinism, and the other one a goitre. One of the children had darker skin than usual, without any other features suggestive of inadequately controlled hypothyroidism. She asked whether the present therapeutic agent, thyroid (4 grains daily), should be replaced by the equivalent dose of thyroxine in this case.

Dr. Wettenhall recommended the change to thyroxine, pointing out that dry thyroid deteriorated considerably in hot weather.

Dr. J. H. Colebatch asked why Dr. Wettenhall recommended a period as long as three months to achieve the final optimal dose of thyroxine. That was in excess of the time taken to introduce maintenance levels of replacement therapy in other endocrinopathies.

Dr. Wettenhall said that he was probably being unduly conservative and bowing too much to tradition. A shorter period was probably more satisfactory.

PROFESSOR W. B. MACDONALD (Perth) drew attention to the cretin who presented with features of intestinal obstruction and in whom the true diagnosis might be overlooked unless kept in mind, and commented that in his experience the only time that heart failure had followed treatment of a cretin with thyroid was in the case of a baby with a congenital heart defect. He believed that text-books overemphasized the risks of producing heart failure with therapy.

Professor Hallman commented that prolonged jaundice in the neonatal period was a not uncommon mode of presentation of hypothyroidism.

Professor Dods said he could recall a few humiliating experiences with infants jaundiced in the new-born period owing to hypothyroidism.

Dr. Wettenhall agreed that such a presentation was not infrequently seen. However, he pointed out that the skin pigmentation in older children was due to carotene, not bilirubin.

[1] *Lancet*, 1961, 1: 329.

Recent Trials of Measles Vaccine.

DR. N. GRAY (Melbourne) read a paper entitled "Live Virus Measles Vaccine—The Current Situation".

Dr. Gray said that in 1954 Enders and Peebles had demonstrated cytopathogenic changes in tissue culture inoculated with measles virus. Complement-fixation and neutralizing antibody techniques thereupon developed allowed accurate laboratory observation of the effects of infection upon susceptible individuals. The vaccine used in the trials described in the present paper had been developed by serial passage in human kidney and amnion cell cultures and chick embryo cell cultures of the Edmonston strain of measles virus.

Clinical trials were carried out on 171 susceptible children. Eighty-three *per centum* had fever and 48% had a rash. Catarrhal signs and Koplik's spots were notably infrequent. Serological response was seen in 96·5% of cases. In 39 children so far challenged by contact with community strains of measles complete protection had been demonstrated.

Whether measles encephalitis would occur with the vaccine was uncertain. The lack of viræmia caused by the vaccine strain, and its inability to propagate in monkey central nervous system, suggested that cerebral involvement due to viral invasion of central nervous system was unlikely. Gibbs had shown that specific electroencephalographic changes seen in 51% of unmodified cases of measles were absent in 28 children infected with the vaccine strain.

Measles vaccine was currently experimental, but was, as tested so far, free of undesirable side effects; it induced a mild illness, the time of which might be selected, and apparently offered satisfactory protection clinically and serologically. Further attenuation was possible, but loss of potency might result. Encephalitis seemed unlikely to follow inoculation with the present vaccine strain, but that was not yet proven.

This paper is to be published in full elsewhere.

DR. H. MCLORINAN (Melbourne) said he believed that Dr. Gray's paper demonstrated well the points in favour of the vaccine, and that his results did not suggest any significant risk of dangerous complications, such as encephalitis. Most pædiatricians should welcome the vaccine and would use it widely. The maternal reaction might not be such an enthusiastic one, but if the Victorian response to the influenza vaccine was a guide, the outlook was optimistic.

Neonatal Intestinal Atresia.

A discussion on neonatal intestinal atresia took place under the chairmanship of DR. R. N. HOWARD (Melbourne).

Dr. Murray Clarke was asked to open the discussion and he pointed to the improved outlook in such children. That was due to: (i) early diagnosis, and especially the awareness among his colleagues of intestinal obstruction as a cause of vomiting in neonates (a more exact location of the lesion resulted in less need to eviscerate the child); (ii) improved anæsthesia; (iii) improved transfusion and electrolyte therapy; (iv) improved technique. Nixon (of Great Ormond Street) had shown how the upper, dilated pouch was incoordinate and needed excision. Dr. Clarke pointed to Professor Lowe's hypothesis of intrauterine strangulation as the cause.

The need to eviscerate was discussed and most surgeons did not believe it was a shocking procedure if done carefully. It was important to search for further abnormalities in the small bowel. Technically it was difficult to check the large bowel in the same way. However, a second atresia in the large bowel was very rare.

Physiological actions were also discussed. DR. F. D. STEPHENS (Melbourne) mentioned that in the dilated, upper portion of a ureter above a partial obstruction there was central retrograde flow of urine. That was not a retrograde peristalsis, and he wondered if the same phenomenon occurred in the gut. DR. PETER JONES (Melbourne) spoke of the two types of contraction in the gut as pointed out by Nixon, namely (i) peristalsis, and (ii) stripping action contraction. It was the latter that propelled bowel contents forward, and in dilated bowel that mechanism was inefficient. Dr. Charlotte Anderson was asked to comment on the amount of bowel that could be safely removed. In reply she said she believed up to 50% of small bowel could be removed. Important points were to leave the ileo-caecal valve in neonates. After resection there were often frequent

motions and the absence of the valve made that worse, as it allowed too rapid flow into the colon. In such cases it was better to increase the oral intake than to switch back to intravenous fluid therapy. Ileo-transverse anastomosis in neonates gave more trouble, owing to the turbulence and colonic flora above the narrowing. Turbulence caused diarrhœa, poor absorption, anæmia and so on. Isoperistaltic anastomosis limited such turbulence. She was in favour of resecting the dilated upper loop. She believed a functional abnormality probably existed in neonatal obstruction of that type. Dr. Clair Isbister mentioned that sucking was a great stimulus to peristalsis and early feeding was important. Dr. Hiller reminded those present of the importance of allowing air to pass into the lower bowel in the new-born before making a diagnosis from an X-ray film.

DR. D. DEY (Sydney) said that as far as the surgical technique was concerned, most surgeons resected the dilated, upper blind end before anastomosis. However, he did not resect the upper pouch (removing the lower inch only), but into the portion of gut above the anastomosis he inserted a rubber catheter as an enterostomy, and by such means deflated the gut. He fed the children early, and had no evidence of residual dilated gut in such cases. Dr. Steigrad agreed that non-resection of the dilated pouch gave just as good a result. Dr. Cohen believed, on the evidence of œsophageal atresia, that non-resection was satisfactory. Dr. Jones pointed out that the neurogenic supply of the œsophagus was different from that of the small gut. Dr. Cohen mentioned the importance of temperature control by an electric rectal thermometer. Evisceration caused a marked drop in the temperature, and he recommended that a warm towel or electric blanket should be used along with control by the rectal thermometer. That control should be continued in the ward until the temperature was stabilized. Most surgeons carried out a one-layer anastomosis and felt that was quite sufficient. Dr. McKay asked if anyone knew of complications due to kinking when an anastomosis was right-angled, and was answered in the negative. DR. E. DURHAM SMITH (Melbourne) asked if a "Polythene" tube crossing the anastomosis had any value. Most surgeons felt that such tubes were not successful and Dr. Howard cited a case in which such a polythene tube had perforated the gut.

Dr. Isbister asked whether a resolution could be passed stating that the treatment of such children be carried out only in children's centres which carried trained staff at all levels.

It was felt that personal propaganda, the publishing of figures and improvement in the treatment given by individual doctors were more important at the present stage.

Wilms' Tumour.

A discussion of Wilms' tumour was limited owing to a shortage of time, and only DR. R. N. HOWARD (Melbourne) was able to speak. He made special reference to chemotherapy and the surgery of pulmonary metastases. As his paper was the basis of an article to be published shortly it was not recorded in the present report.

Hypokalæmia, Hyperlipæmia and Tetany.

DR. D. B. CHEEK and DR. K. TURNER read a paper entitled "Hypokalæmia, Hyperlipæmia and Tetany — A Metabolic Derangement Illustrating the Probable Rôle of Lipids in Electrolyte Transport".

Dr. Cheek and Dr. Turner discussed a patient, a female, aged 11 years, who presented with a two-year history of periodic tetany, carpo-pedal spasm and no muscle paresis. She was found to have hypokalæmia at all times and raised plasma bicarbonate concentration, hypochloræmia and occasional hyponatræmia. Her plasma pH was never greater than 7·45. Her blood pressure and liver, renal and adrenal functions were all normal, except that she could not concentrate her urine above 580 milliosmoles per litre. Potassium loads were not retained, nor were they of dramatic therapeutic benefit. There was a tendency to a reduction of extracellular volume and an increase in cell water content. Loss of total body chloride and extracellular sodium was demonstrated by volume studies. Analysis of a muscle biopsy yielded data suggesting a disturbance in sodium/potassium transport.

There was only a slight reduction (14%) of muscle cell potassium when the plasma concentration was 1·9 mEq/l. Moreover, in the presence of a raised plasma bicarbonate level there was a 33% decrease in cell sodium instead of the expected increase.

Coincidently a hyperlipæmia of the transport type was exposed, with an increase in fatty acid and triglyceride concentration in the plasma. Phosphatidyl ethanolamine concentration was increased in the plasma. It was considered that the disturbance in lipid metabolism was related to the electrolyte disturbance, with possible effects on the sodium pump of the muscle cell. When 100 rats were given various natural oils, triglycerides or fatty acids it was found that certain fatty acid esters could remove 50% of the muscle cell sodium in three hours.

This paper is to be published in full elsewhere.

Professor W. B. Macdonald commented on the importance of elucidating fundamental biological relationships by studies on patients such as the case described by Dr. Cheek and Dr. Turner.

DR. I. MCDONALD (Canberra) said he felt that it was rash to assume that carrier mechanisms such as the sodium pump should be activated by lipid factors. Dr. McDonald suggested that experimental study of the interrelationships discussed would be more significant if isolated tissues were used. In the whole animal variables such as the adrenal cortical activity and serum protein levels made analysis of results more complex.

Dr. Cheek replied that the findings in his patient defied Darrow's biological equilibrium, and he found that difficult to explain except on the basis of a transport defect.

PROFESSOR W. V. MACFARLANE (Canberra) pointed out that the increased fatty acid levels in the patient were unexplained. The presence of a fat-mobilizing substance—for example, from the pituitary—would be one theoretical explanation. He also commented on the finding of reduced intracellular levels of both sodium and potassium, which finding was not in accord with conventional ideas of exchange of those ions. Professor Macfarlane mentioned that increased work was done by a number of tissues when fat was present in the medium (for example, transport maxima of the kidney for P.A.H., glucose and potassium were increased in the presence of butyrate) and suggested that investigation of renal tubular transport in the patient discussed might yield rewarding information.

Microdissection of Baby Kidneys.

DR. DORA BIALESTOCK (Melbourne) read a paper on "Microdissection Studies in Baby Kidneys—Scope and Application".

Dr. Bialestock discussed the historical background and technical details of the method of microdissection as applied to baby kidneys.

Use of the method was demonstrated by slides of nephrons from cases of pyelonephritis, polycystic disease, hydronephrosis, anæmia with renal disease and the nephrotic syndrome.

She said the method was of value because data that might not be easy to appreciate by routine histology could be obtained. The entire nephron could be studied in its length at the one time and the site of abnormalities clearly defined. The abnormal nephron could be measured and compared quantitatively with the normal. The site and rate of normal growth could be studied. Study of the dissected nephrons had helped in the interpretation of histological sections.

In the baby kidney the method had revealed the presence of multiple bizarre abnormalities, but at present dogmatic interpretations of the significance of those changes and their associated clinical manifestations was not warranted.

This paper is to be published in full elsewhere.

Dr. Southby congratulated Dr. Bialestock on her painstaking work and asked how long it took to dissect a nephron.

Dr. Bialestock said that the time of dissection varied, the most important factor facilitating dissection being an optimal degree of maceration of the specimen.

Dr. Cheek asked Dr. Bialestock if urinary concentrating ability had been estimated in the patient whose nephrons had a short loop of Henle.

Dr. Bialestock replied that the baby had achieved a urinary specific gravity of 1018 on one occasion, but the specific gravity was usually about 1010.

Dr. Taft asked if abnormal structures were found in "normal" kidneys, or if they appeared in experimentally produced pyelonephritis in animals.

Dr. Bialestock had not found abnormalities in "normal" kidneys and knew of no relevant work on experimentally produced lesions.

DR. F. D. STEPHENS (Melbourne) pointed out that many children previously regarded as having hypoplastic kidneys could now be regarded rather as having dysplastic kidneys.

Congenital Nephrotic Syndrome.

PROFESSOR NIILO HALLMAN (Finland) read a paper entitled "Congenital Nephrotic Syndrome".

Professor Hallman described a series of 26 children with congenital nephrotic syndrome examined and treated at the University Children's Hospital in Helsinki. The clinical symptoms of the disease were exactly the same as those of genuine lipoid nephrosis: the formation of œdema, a special predisposition to ascites, changes in the composition of the serum proteins, proteinuria, a low urea nitrogen level, elevation of the serum cholesterol level and normal blood pressure. However, more symptoms of chronic nephritis appeared when the disease was of longer duration.

The congenital nephrotic syndrome was distinguished from ordinary nephrosis by its early onset, familial occurrence and invariably fatal termination. Steroids had never had any influence on the disease. The symptoms, œdema and proteinuria, were sometimes established immediately after birth and at the latest within two to three months. Protein was usually present in the first urine sample examined. Proteinuria might have been demonstrable immediately after birth had the patients been examined carefully enough.

When a congenital disease was involved, pregnancy and factors pertaining to delivery must naturally be considered. The mother was found to have had slight symptoms of toxæmia of pregnancy in six cases and allergy in one case. In the cases in which information was obtained concerning the placenta it was stated to have been distinctly larger than normal in 12 cases and abnormally large (the weight range being 700-1500 grammes) in all the cases in which it was weighed. Unfortunately it was not possible in a single case to make a more detailed examination of the placenta. The majority of the infants were born two to six weeks prematurely. In only three cases was the birth weight over 3 kg., and none of those three children were in the "large baby" class. Some infants showed slight symptoms of neonatal asphyxia.

The family history was very interesting. In spite of the most careful studies no consanguinity, even remote, was established between the parents in a single case. Moreover, the families came from different parts of Finland. Ten families had more than one child affected with the disease.

If one considered the families in which one child only was known to be affected, and omitted the families in which that child was the only one, one found a relatively high incidence of mortality in the premature infants—a mortality rate of 26%. That percentage was many times the normal incidence for premature infants. That clearly suggested that there was in the children of such families something peculiar that caused prematurity and death. It was tempting to assume that the prematurity and neonatal mortality were associated in some way with the congenital nephrotic syndrome. That was, of course, unsubstantiated surmise.

An autopsy had been performed on all the children who had died. The final cause of death was infection (principally respiratory) in all cases. A typical finding in all was fatty metamorphosis in the liver and œdema of the organs. The renal findings were also fairly characteristic. The kidneys were either normal in size or fairly large—never small and fibrotic. In the case of children who died after a prolonged course the renal capsule was adherent, but in the other cases it was easy to detach. A typical histological feature was the cystic dilatation of the renal tubules, which was easily apparent even at low magnification. The cystic change was localized principally to the proximal tubules. The epithelium was foamy and eosinophilic in the dilated parts and elsewhere in the proximal tubules. Histochemical dehydrogenase staining showed a normal range of enzyme activity in the dilated tubules. Many proximal tubules contained a fine granular material, irrespective of whether they were dilated or not. Fatty deposition and signs of degeneration were seen sometimes. The collecting tubules were mostly normal in appearance. The peritubular interstitial tissue was increased in the longer-standing cases. The arteries and veins seemed in the main to be normal in structure.

Six cases were studied by electromicroscopy. The changes were similar in all the glomeruli studied, but were not equally distinctly demonstrable in each case. The space of Bowman generally seemed to be of normal width, suggesting that that nephron was not blocked. Thus pressure was probably not the cause of the established changes. The primary morphological changes were found in the glomerular epithelium. The so-called foot processes of the epithelial cells seemed to become shortened and gradually to disappear completely, probably by merging of damaged foot processes. The protoplasm of the epithelial cells thus came to cover the basement membrane of the capillary as a uniform thick layer and the pores between the epithelial cells disappeared. With continuation of the process, vacuoles appeared in the cytoplasm of the epithelial cells, and the cytoplasm of the peripheral epithelial cells adhered to Bowman's capsule. When the disease had continued for a longer time, degenerative changes were seen in the basement membrane. Endothelial cells showed a vacuolization similar to that of the epithelial cells. The vacuoles contained a light-refracting material like that in the capillary lumen.

The morphological study included microdissection of nephrons, performed in 22 cases by Darmady's method. The report on that work was in the process of being published.

In all 22 cases a typical lesion was shown in the proximal convoluted tubules — irregular, wide, cyst-like dilatations alternating with atrophied segments. There was marked cellular hyperplasia in the epithelium of the tubular dilatations. It was worth noting that that kind of cellular increase in the epithelium had not been observed in tubules dilated by obstructive factors. In 14 of the cases of congenital nephrosis a narrow, atrophic neck part of the proximal tubule was found, varying in length from 0·11 to 0·36 mm.

The heavy fatty degeneration found in the nephrons was limited to the proximal part of the tubule. In the rest of the tubule the epithelial pattern appeared to be quite normal. In 14 of the cases slight dilatations were seen in the distal convoluted tubules. Those dilatations were lined with normal epithelium and did not in any way resemble the irregular cystic dilatations in the distal convolutions from the case of microcystic renal disease reported by Oliver.

Professor Hallman then discussed theories of the ætiology of the disease. He stated that a commonly accepted theory of the genesis of nephrosis in man was that the renal damage was the result of auto-immunization, the patient having formed antibodies against his own kidney. That was an hypothesis based principally on animal experiments. It seemed unlikely that the new-born, who were known to be immunologically unresponsive, were able to form sufficient antibodies to cause an auto-immune disease. Another possibility was that the disease might begin *in utero*, and be caused by antibodies produced by the mother and transported via the placenta into the fœtus. The great number of premature infants among children with congenital nephrotic syndrome, and the large size of the placenta, indicated an onset of the disease in the fœtal period. A large placenta was suggestive especially of some immunological process. Consequently one would have expected the disease to occur also in the mother, but toxæmia of pregnancy in mothers delivered of a child with congenital nephrosis was not very common. Another possibility was that of antibody formation and auto-immunization induced by the placenta. The investigations of Professor Hallman's group lent support to the antibody theory. Kouvalainen, the principal worker, had been able to demonstrate in two cases, by means of Ouchterlony's gel-diffusion test, antibodies against renal, placental and liver tissue in the blood of diseased children. That could not be shown in other new-born infants. It was known from animal experiments that there were antigenic similarities between placenta and kidney tissue. Anti-liver serum was said to possess some nephrotoxic properties in laboratory animals.

Professor Hallman's group had also conducted a number of experiments in animals to find out what happened to the rat fœtus if the so-called Masugi nephrosis was induced in the mother by the injection of nephrotoxic serum into its blood. Other animals were treated with an aminonucleoside, puromycin, which could also cause the nephrotic syndrome in rats. ^{131}I-labelled nephrotoxic serum could be demonstrated profusely in the maternal kidneys and also in the placenta a few hours later. Labelled globulin was found diffusely in the different organs in three to five hours, and also in the fœtus.

Serum injected in the early stages of pregnancy caused abortion in the rat in the majority of the cases. When the serum was injected during last days of the pregnancy the rat young were usually healthy, but sometimes very undernourished. Aminonucleosides also caused abortion or death in the first days of life. Œdema sometimes occurred in the surviving animals. Histological examination of some animals showed quite distinct dilatation of the tubules, and of others revealed complete nephrolysis. The serum choles-

terol level was elevated in some surviving rats, but no definite changes suggestive of nephrosis (for example, in the serum protein levels) were established. If the young recovered from the first phase there was a good cure rate. Those investigations were still in progress, but it could be said already that they indicated immunization or the possible existence of nephrotoxic reagents, at least in rats. The results could not, of course, be considered valid for man as they stood.

Dr. Southby remarked that some factor acting early in intrauterine life seemed likely to be the cause of neonatal nephrosis. He asked Professor Hallman whether viral infection in early pregnancy was a possible cause.

Dr. Kate Campbell mentioned the number of similarities between neonatal toxoplasmosis and congenital nephrosis. She asked whether toxoplasmosis could be an ætiological factor.

Professor Hallman, in reply, said that both viral infections and toxoplasmosis had been looked for, but no evidence to implicate them had been found. He agreed with the suggestion that the causative factor probably began to act early in pregnancy.

Treatment of Bronchiolitis with Hydrocortisone.

DR. M. MCGEORGE (New Zealand) read a paper entitled "Hydrocortisone in the Treatment of Bronchiolitis in Infancy".

Dr. McGeorge stated that bronchiolitis commonly represented the first stage in the development of an acute lower respiratory tract infection. The basic lesion was œdema and mononuclear infiltration of the bronchiolar wall, together with excessive mucus production. In young infants that might result in severe respiratory distress, and even death from asphyxia within a few hours of onset. In older children obstructive features tended to be less severe, and secondary bacterial invaders then gave rise to bronchitis, bronchopneumonia and segmental pulmonary collapse.

Symptoms indicative of severe obstruction in infants included restlessness, cyanosis, tachypnœa and lower costal indrawing on inspiration. Examination showed the features of obstructive emphysema without consolidation. Although the majority of victims of bronchiolitis recovered, very severe cases were occasionally encountered, particularly in young infants, in which there was no response to treatment with antibiotics, oxygen and increased humidity, and in which an asphyxial type of death occurred with startling rapidity.

Hydrocortisone hemisuccinate, given in repeated high dosage by intramuscular injection, was therefore tried in the case of infants showing signs of peripheral respiratory obstruction, the object being to suppress the inflammatory reaction in the bronchioles, and thus lessen mechanical respiratory obstruction. One hundred milligrammes of hydrocortisone hemisuccinate were given every four hours, irrespective of the weight of the infant, until there were definite signs of improvement, after which the drug was rapidly withdrawn. Chloramphenicol (50 mg. per kilogram per day in divided doses) was given at the same time to control bacterial spread.

Ten consecutive infants with bronchiolitis had been successfully treated in this manner; five of the cases were severe and three infants critically ill on admission to hospital. Total hydrocortisone dosage ranged from 275 to 1525 mg., given over periods of from 18 hours to five days. It was recommended that the use of hydrocortisone in such a manner should be considered as an additional measure in the early treatment of bronchiolitis in infants in whom respiratory obstruction had developed or appeared to be developing.

Dr. Jones asked whether any cases of emphysematous lobe had caused confusion in diagnosis and whether there was any place for tracheostomy in bronchiolitis, in view of the high ratio of dead-space air to tidal air.

Dr. McGeorge replied that no cases of emphysematous lobe had been encountered, and that tracheostomy had not been performed.

DR. I. S. WALLMAN (Perth) asked if any recurrences had occurred in the series, and if there was any family history of allergy.

Dr. McGeorge said there were no recurrences, and there was no significant increase in incidence of allergy in the family.

Professor De Silva mentioned that bronchiolitis was a common problem in Ceylon. He stated that in his experience the disease was encountered more commonly in well-nourished infants, and that mist therapy had been accompanied by improvement in some cases. Professor De Silva had used prednisolone without any impressive response, and asked Dr. McGeorge if he had used steroids other than hydrocortisone.

Dr. McGeorge could quote no personal experience of results of prednisolone therapy. He also had noticed the greater incidence of chubby babies affected. Dr. McGeorge expressed an antipathy to wetting agents in therapy.

DR. GOODELL (United States of America and Sydney) expressed the view that bronchiolitis seemed to occur more commonly in temperate zones. In his experience high oxygen concentrations were the most beneficial therapeutic measure.

Dr. McGeorge agreed that oxygen was important. Estimations of oxygen concentration had not been done in his series.

DR. S. STENING (Sydney) asked if it was felt that such cases had a viral cause, and what was the rationale of using hydrocortisone.

Dr. McGeorge replied that hydrocortisone was used in the effort to prevent an inflammatory reaction of any ætiology.

Accidental Digitalis Poisoning.

DR. R. FREEMAN (Sydney) read a paper entitled "Accidental Digitalis Poisoning in Childhood" (see page 655).

DR. D. STUCKEY (Sydney) said he believed that there was a good deal to support the theory that delayed vomiting was an important adverse factor in the fatal case. He spoke also of the increasing awareness of the danger of hypokalæmia in patients having digitalis therapy. Dr. Stuckey hoped that the report of those cases of poisoning would not dissuade physicians from using digitalis, which was a very valuable drug. The dosage in the cases of poisoning had been about 10 times the accepted therapeutic dosage.

PROFESSOR G. MAXWELL (Adelaide) related details of an infant with transposition of the great vessels and cardiac failure, who had become addicted to digoxin elixir, and had finally poisoned himself. Professor Maxwell asked if any of Dr. Freeman's cases occurred in a similar way.

Dr. Freeman replied that all the children reported had been free of heart disease. Cases of accidental overdosage in hospital had been excluded.

Congenital Cardio-Vascular Disease.

DR. GEORGE WESTLAKE (Melbourne) read a paper entitled "Defects of the Atrial Septum" (see page 659).

DR. A. W. VENABLES (Melbourne) and DR. P. G. JONES (Melbourne) presented a paper entitled "Aortic Stenosis with Heart Failure in Infancy" (see page 665).

DR. IAN S. WALLMAN (Perth) read a paper entitled "Coarctation of the Aorta in Infancy" (see page 668).

Professor Maxwell agreed with Dr. Wallman about the importance of palpating the femoral arteries in infants. In general he agreed that surgery should be undertaken early. Professor Maxwell had seen five children in whom cardiac catheterization had been carried out before surgery, and he believed it should be carried out to determine the pressures even if cardiac failure was present. It also gave a better idea of the prognosis. Patients with marked pulmonary hypertension did not do well and of those that came to autopsy only coarctation and pulmonary sclerosis were discovered. He doubted if the pulmonary hypertension was simply a reflection of the increased end-diastolic pressure.

Dr. Venables reported 43 cases in six years of patients under 12 months of age, of whom 27 had cardiac failure. Of the 19 who died all but one had a patent ductus and all had either a significant associated cardio-vascular anomaly or some other serious disease. Of the eight survivors (not fully investigated) only two appeared on clinical grounds to have other cardiac lesions. He could understand the experience of Nadas, who reported a number of survivals, because the great proportion of those seen at the Royal Chilren's Hospital, Melbourne, during the previous 18 months had been without other cardiac lesions and had survived.

Dr. Cohen, in reference to Dr. Westlake's paper, stated that when possible repair of a defect should be done under

vision. He therefore preferred to repair atrial septal defects on the pump, which had, however, the disadvantages of complexity, the need for blood and so on. In dealing with aortic stenosis in infancy he would prefer the supravalvular approach under hypothermia. With regard to coarctation in infancy Dr. Cohen believed a selective approach the correct one, and mentioned that the majority of patients had done well with conservative management. He reiterated the importance of dividing the lesions into pre-ductal and post-ductal types, because of the different prognosis.

Dr. Wettenhall congratulated Dr. Venables on diagnosing one case of aortic stenosis of which he had personal knowledge and asked how common the condition was. Dr. Venables replied that during the six-year period one other case had been picked up in the autopsy room.

Dr. Stuckey said that the papers had drawn the attention of those present to the fact that there were serious defects which were remediable in the neonatal period.

Dr. Westlake commended Dr. Jones on his technique of compressing the aorta to encourage blood to enter the coronary arteries. He did not believe hypothermia had a place, for it was irritating to the heart and deprived it of its blood flow. The atrial-well procedure for the repair of atrial defects had the advantages of the infliction of less trauma, the necessity for only one bottle of blood and the patient's ambulation on the second day and discharge from hospital on the tenth day.

Dr. Jones supported Dr. Westlake in his views.

Congenital Heart Disease and the Family.

PROFESSOR G. MAXWELL (Adelaide) read a paper entitled "The Impact of Congenital Heart Disease on the Family".

Professor Maxwell discussed the findings of social workers who investigated the effect on the parents and siblings of children diagnosed as suffering from congenital heart disease. Fear was the commonest type of initial reaction seen in the parents, with a variety of other types, including hostility, resentment and even relief, occurring less frequently.

A notable finding was the very poor understanding of the disease by the parents. At times this was because no explanation, or an inadequate one, had been given by the doctor, but even after one or more adequate explanations many parents did not comprehend the cause or nature of the disease.

Life in the home was often altered after the diagnosis of congenital heart disease in a child had been made. The affected child was often spoiled, and sibling jealousy was common. Marital relations were usually unaltered, but sometimes became worse or better.

Professor Maxwell emphasized how important it was for the doctor to realize all the factors which ensued on the diagnosis, and to attempt to help adjustment in the family by adequate and repeated explanation.

PROFESSOR V. L. COLLINS (Melbourne) commented that the problems outlined by Professor Maxwell occurred in many other diseases as well. He recalled the words of Sir James Spence, who had pointed out that the main duty of the consultant after diagnosis was that of explanation and advice.

Dr. Goodell discussed the emergence of the "new pædiatrics". He emphasized how important was listening to the parents. If their problems were appreciated, then explanation became more satisfactory. Preventive medicine could be interpreted to include prevention of family fears and so on in such circumstances.

Professor Hallman mentioned a survey similar to that of Professor Maxwell carried out in Helsinki by a team which included a psychiatrist, a psychologist, a surgeon and a physician. The results were essentially in agreement with those of Professor Maxwell.

Professor Stapleton spoke of the key rôle played by the general practitioner in handling many of the problems discussed. He also stressed that the pædiatrician and surgeon should be prepared to relinquish parts of their patients' care to those more versed in dealing with family relationships when the occasion arose.

Speech in Children with Cleft Palate.

A discussion of speech in children with cleft palate took place under the chairmanship of DR. J. STEIGRAD (Sydney).

Dr. Dey commenced the discussion by mentioning the difficulty in the assessment of speech, and how in Sydney an attempt at classification had been made. He said that such a classification should be simple and not over-burdened with too many subgroups, and that the terms used should be understood by everyone. The classification must be a written one, as tape recordings and so on carried too many disadvantages and did not necessarily give a faithful reproduction. Not only could an assessment be made after a cleft palate repair, but also any improvement following a secondary operation could be noted.

The classification consisted of four groups—namely, good, adequate, intelligible and unintelligible—with five subgroups to each major group of tonal quality, air escape, consonants, articulations and tongue and lip movements. An abnormality could be noted in one of three degrees.

Dr. Steigrad supported such a classification.

DR. T. Y. NELSON (Sydney) said he believed the speech therapist should make the classification and most surgeons agreed, though it was suggested the surgeon himself should also make a classification to aid his own follow-up. In Sydney the classifications of both parties had been found to agree roughly. Dr. Nelson suggested that it should be called "Cleft Palate and Allied Conditions: Classification of Speech Results".

DR. W. S. RICKARDS (Melbourne) mentioned the importance of intelligence, the stage of maturity, deafness, occlusion, psychological upsets and so on in speech disorder. It was agreed that such factors should be noted and referred to the department concerned, but that the addition of such to the classification would make it cumbersome. Dr. Rickards spoke of the importance of the liaison between the speech therapist and the mother and child, and how in Melbourne the mother's morale had improved notably, owing to the expectation of good speech in her child.

An interstate classification was believed to be desirable and an approach was to be made, firstly, to those clinics not represented, in order to determine their views, and later to the schools of speech therapists.

Out of the Past.

TREATMENT OF THE INSANE IN VICTORIA.[1]

[From the *Australasian Medical Gazette*, April 30, 1903.]

WE make the following abstracts from a report which the Chief Secretary has received from Drs. Jamieson and Joske, two of the official visitors to the Melbourne metropolitan asylums. Their aim has been to present an account of the institutions as they are, not passing over their defects, and yet trying to be fair. Most, if not all, of the genuine defects recently pointed out have been the subject of remark, and many of them repeatedly, in the official reports. It is admitted that the main building at Kew is badly planned, the construction being so defective, and the means of escape so deficient and badly placed, that an outbreak of fire might lead to a serious catastrophe. As a result of continuous overcrowding, rooms that are little better than wide corridors are used not only as sitting and recreation rooms, but also have to serve as dining-rooms. Another result of overcrowding is that some of the yards are habitually too full, and they are insufficient to allow of proper classification and separation of patients.

Seclusion and restraint are in the hands of the medical superintendents, without whose direction their use is forbidden. Seclusion may be a legitimate measure of treatment and opinions may, and do, differ among authorities about it. As to restraint, there is practically a consensus of opinion that it should be kept at a minimum, and in its ruder forms abandoned. For restraint may be in various forms: (1) Mechanical, by jackets and other appliances; (2) by mere force of hands; (3) model, by personal influence and persuasion; and (4) medicinal, by means of sedative drugs. Of them all, the third should, theoretically, be alone in use; but, if so, there must manifestly be a large and efficient staff of attendants. In practice, there must and will be some amount of manual restraint needed. Most of the restraint in use is of a very harmless kind, and aims merely at keeping certain patients from injuring themselves or destroying their clothing.

Recommendations are made that at each asylum there should be a small detached building for the prompt isolation

[1] From the original in the Mitchell Library, Sydney.

of infectious cases; that it might be advisable to leave all cell doors unlocked at night, as could easily be done with a sufficient increase in the number of night attendants; and that there should also be a system of electric tell-tale clocks. The doctors consider that something should be done at the earliest possible date to provide a suitable receiving house. Separate provision should be made without delay for patients whose friends are willing to pay for the accommodation. Another recommendation is that the superintendent of each asylum should be held responsible for all that takes place in his asylum. He should be under control of a board of management, which should have full control of the whole department. Such a board might consist of the Minister in charge of the department, the inspector and a capable business man. The final recommendation is that one of the metropolitan asylums should be converted into a strictly curative hospital. This would mean a great reduction in the number of inmates, and of necessity the erection of other buildings elsewhere.

Correspondence.

GENERAL PHARMACEUTICAL BENEFITS.

SIR: Mr. Neil, in his letter published in THE MEDICAL JOURNAL OF AUSTRALIA for September 30, states that I am comparing the British wholesale price of "Androstanalone" with the Australian retail price. This is not so. In my letter I quoted the price of £A12 7s. 0d., which is the figure mentioned in the Department of Health Schedule of Benefits as being the dispensed price for maximum quantity, i.e., 100 oral tablets. However, on inquiry from the local chemist, I find that the *retail* price of this product is no less than £A13 18s. 0d., which leaves a further £A1 11s. 0d. to be accounted for, the difference being not £7·18s. 6d. (Mr. Neil's figure), but £9 9s. 6d. Incidentally, it seems a little odd that, as Mr. Neil asserts, the wholesale price should be quoted in the *British Medical Journal*. His final remark about a higher standard of living is untrue and irrelevant.

Yours, etc.,

Beulah, Victoria.
October 4, 1961.

T. W. HERDMAN PORTER.

AN APPEAL.

SIR: The Royal Children's Hospital requires a copy of its 46th annual report, covering the years 1914-1915. It would be appreciated if anyone possessing a copy of this report would contact the Manager of the hospital.

Yours, etc.,

Royal Children's Hospital, Melbourne, N.3.
October 6, 1961.

W. C. FEINT, Manager.

BENDROFLUAZIDE IN PREGNANCY TOXÆMIA: A SHORT CLINICAL TRIAL.

SIR: It is considered desirable to publish the results of a trial of bendrofluazide (benzylhydroflumethazide) conducted at the Queen Victoria Maternity Hospital in 1960-1961, in view of recent reports of the successful use of this diuretic for indications other than œdema in preeclamptic toxæmia.

A series of 50 consecutive cases admitted to the ante-natal ward on one clinic had the drug administered in doses of 5·0 mg. daily over an average period of five days, or until diuresis was complete. Where resistance occurred or in essential hypertension the drug was then continued in daily dose of 2·5 mg. Administration with breakfast resulted in diuresis during daytime, and no undesirable side-effects were recorded with this method. In two cases some nausea resulted when the tablet was administered on an empty stomach. Of the 50 cases, 40 had previously been given chlorothiazide 0·5 gramme twice or thrice daily for intervals of up to 21 days in the ante-natal clinic, prior to admission, and were therefore regarded as relatively resistant to chlorothiazide. Three cases had, in addition, been given acetazolomide during this time.

Results.

Forty resistant cases:

Preeclamptic toxæmia, 38 cases.
Essential hypertension, 2 cases.

Initial œdema:

Mild or moderate, 30 cases.
Severe, 5 cases.
Nil, 5 cases (2 hypertensive).

Diastolic blood pressure:

Maximum, 110 mm. of mercury.
Minimum, 85 mm. of mercury.

Weight change after five days:

Increase, 6 cases.
No change, 8 cases.
Loss, 26 cases.
Maximal gain, 4 lb. (mean, 2 lb.).
Maximal loss, 9 lb. (mean, 3 lb.).

Diuresis (positive fluid balance in any 24 hour period):

None, 8 cases.
Successful, 32 cases.
Maximum, 90 oz.
Minimum, 12 oz. (mean 33·5 oz.).

Duration:

Maximum, 11 days.
Minimum, 2 days.
Mean, 3·3 days.

Conclusions.

Bendrofluazide is considered to be a safe diuretic for use in pregnancy toxæmia. It is claimed to have a potency nearly ten times that of chlorothiazide, and to be associated with less potassium excretion. No deleterious side-effects were found, and the single morning dose resulted in satisfactory daytime diuresis.

In a small series of relatively resistant cases hospitalized for pregnancy toxæmia, successful diuresis occurred in 80% and weight loss over five days in 65%. Diuresis occurred in one of the two cases of essential hypertension without, however, any loss of weight.

The bendrofluazide used in this series was supplied by Boots Pure Drugs (Aust.) Ltd. It is desired to thank Dr. G. T. Gibson, on whose patients this trial was conducted.

Yours, etc.,

Queen Elizabeth Hospital, Woodville, South Australia.
October 5, 1961.

IAN H. F. SWAIN.
Department of Obstetrics and Gynæcology, University of Adelaide.

THE ABUSE OF ANTIBIOTICS

SIR: Dr. Babbage's letter dated September 7 is to be highly commended. The abuse of antibiotics is widespread, the cost to the Government enormous, and the aid to the poor suffering gynæcologist in treating subsequent monilial infection is always welcome. I, for one, will join Dr. Babbage's "Anti-Antibiotic Association".

Yours, etc.,

19 Gerrale Street, Cronulla, New South Wales.
October 4, 1961.

A. M. MACINTOSH.

CLOSING OF THE RECEPTION HOUSE, DARLINGHURST, NEW SOUTH WALES.

SIR: I wish to advise you that as from November 1 next, it is planned to evacuate what has been known for more than 90 years as the Reception House, Darlinghurst, and in its stead persons suffering with mental illness may be admitted to the newly constructed Admission Centre, Cox's Road, North Ryde, Sydney. Care should be taken, therefore,

to ensure that medical certificates given in the form set out in Schedule 2 of the *Mental Health Act*, 1958, on and after the date mentioned, bear the name of the Admission Centre at North Ryde.

The accommodation at the Reception House, Darlinghurst, has been recognized as inadequate for a considerable time, but excellent facilities and greater accommodation will be available in the new unit, which, as a matter of interest, cost more than £300,000. A further unit of similar design and capacity is under construction, and will, it is expected, be brought into use next year at Rozelle.

As you will surmise, it will be practicable in these circumstances to provide treatment for many of the persons admitted without the need to transfer them to a mental hospital.

In regard to mental services generally, you will no doubt have read of the appointment of the Health Advisory Council and the adoption by the Government of its proposals for an integrated mental health service. The new admission centres, with accent on treatment rather than reception, represent the first step in this direction.

Yours, etc.,

Department of Public Health, 52 Bridge Street, Sydney.
October 3, 1961.

J. D. RIMES, Under Secretary.

DEMOCRACY.

SIR: Events over the past few months, involving the civil service, have provided very salutary lessons to the medical profession of Australia, or at least to those doctors willing to draw obvious conclusions from them. In rapid succession we have had the examples of Government and civil service retribution upon those that dare make public affairs in the service which they consider are in need of correction. I refer to: (i) Dr. Bazeley's suspension and relegation over the Commonwealth Serum Laboratories affair; (ii) Dr. Bailey's vilification by the New South Wales Minister of Health over his disclosures of the Callan Park scandals under parliamentary privilege; (iii) the persecution of a Postmaster-General's Department employee, for his efforts to stop abuses within the department.

Dr. Bazeley and Dr. Bailey should both be thankful that they were not interviewed by the security police and threatened with imprisonment under the *Crimes Act*, as occurred with the P.M.G. employee.

The salaried staff in hospitals, the Government-employed medicos within the health department and elsewhere have been conspicuously silent over these incidents. It would appear that within our profession there is a body of opinion, particularly amongst the younger specialists, who would not look with disfavour upon any moves on the part of the Government to institute a National Health Service, providing that the remuneration were high enough.

It is probable that no voice is heard in support of Dr. Bazeley and Dr. Bailey from these quarters for fear of jeopardizing their advocates' advancement within their departments or within any future Government service.

What does all this mean to the general practitioner and to all those others who wish to retain their freedom? It means that, as potential targets of an N.H.S., our future and our freedom are threatened by a system which penalizes anyone who wishes to think and act independently in the public interest. Fears of being branded as a non-conformist (or worse) often successfully stifle criticism within a department, be it in hospital or Government service. It is interesting to note that these freedoms are not afforded to our British colleagues for fear that "Any doctor who should displease the Minister may be summarily dismissed from the Service. His sole appeal is to the Minister of Health, appeal to the Courts of Law being prohibited by the Terms of Service" (*Brit. med. J.*, January, 1948).

The negligible amount of assistance offered by the profession to any of its members who suffer at the hands of bureaucracy, should they dare to break a regulation, bodes ill for all those who place freedom and justice above economic security. Surely the lack of the fundamental freedom to express publicly what we think is wrong, when it may involve the health of Australia, is too big a price to pay for personal advancement and the debasement of a noble profession.

As I wrote in THE MEDICAL JOURNAL OF AUSTRALIA of August 26, 1961, the time is now ripe for the Australian Medical Association to press for professional privilege in any public utterances made by any of its members in Government service. Without this privilege, the whole status of medicine is in peril, and those who accept such service in this year and generation will be responsible.

Yours, etc.,

339 Church Street, Richmond, Victoria.
October 7, 1961.

CHARLES M. ROSEBY.

TEETH AND CONSTITUTION.

SIR: Over a period of years there are two observations that I have made, and probably noted by other members of our profession. These observations have recurred at not infrequent intervals, coincidental perhaps, but nevertheless, from their frequency it is not unreasonable to assume that they do possess some significance. The first, that certain individuals who possess a definite type of teeth, in that, the teeth are short in length, are closely packed, they have a pearly appearance, look strong, that they are not prone to dental decay. It has been my experience that individuals with the type of teeth described remain free from constitutional disease and live well over the allotted span, that they remain physically and mentally active. This does not mean that people with other types of teeth do not live to a great age; but if the type of teeth described are recognized early in life, then you can predict with a high degree of certainty their future health (all other things being equal). The second, the type of individual who lives to a great age and throughout life enjoys good health, in that they remain particularly free from intraocular degenerate changes. I would be most interested to learn from readers of your Journal if they have had similar experiences.

Yours, etc.,

241 Oxford Street, Bondi Junction, New South Wales.
October 12, 1961.

K. ADDISON.

IODINE FOR PRE-OPERATIVE SKIN PREPARATION.

SIR: It having been suggested to me lately that the risk of iodine dermatitis is great and that its use for skin "sterilization" should be abandoned in favour of one of the modern antiseptics, I write now in search of information from surgeons or observers with many years' experience of the use of tincture of iodine, on this question of whether or not iodine sensitivity is indeed a difficulty of an extent justifying the loss of such a long-proven friend. (E.g., I understand, subject to correction, that tincture of iodine 1% will ensure "virtual sterilization" in 30 seconds.)

It seems reasonable also to request the exclusion of cases where irritation has followed application of tincture of iodine to skin in an already irritated or tender condition.

My own experience, and that of a number of colleagues whom I have questioned, is that iodine dermatitis is exceedingly rare. I do not recall (though admitting memory is fallacious) having one of my own in a quinquennium.

Yours, etc.,

143 Macquarie Street, Sydney.
October 12, 1961.

C. C. McKELLAR.

Obituary.

HUGH THOMSON RAMSAY.

THE following is an additional appreciation of the late Dr. Hugh Ramsay.

A word from an old friend: Although his career as an anæsthetist is well known to an appreciative circle of colleagues, many did not know Hugh Ramsay in the earlier phase of his medical life. He was not one to

rush the medical course, and who knows that such an approach is not a better one than is forced upon the groaning gyri of the contemporary student? But once a graduate, Hugh showed yet again how little the undergraduate performance may have to do with clinical strength.

He appeared at the Launceston General Hospital, and soon established himself as an outstanding resident medical officer. Naturally he was asked to remain on the staff, and he became an able, dependable and popular lieutenant for the then Surgeon Superintendent, Dr. Clifford Craig. It is small wonder that from this beginning Hugh went on to become a first-class exponent of the specialty of his choice.

He practised in the shadow of some grave difficulties, and if his faults caused irritation, surely there are none who have not forgiven, saddened that his talents, together with his cheerful self, have gone from our midst.

FREDERICK BLOIS LAWTON.

We are indebted to Dr. Walter Summons for the following account of the career of Dr. F. Blois Lawton.

Blois Lawton descended from a medical family. His grandfather John practised in Suffolk; his father Frederick, born in 1831, graduated from Guy's Hospital in 1863 and became house physician to Sir William Gull. Frederick came to Australia in 1868 and practised first at Horsham, Victoria; he then moved to Lancefield. Blois was born there on November 30, 1886, and was educated at Brighton Grammar School; on the accidental death of his father consequent on a fall from a horse, followed in a few years by the death of his mother, Blois was placed in the care of the Head, Dr. Crowther, who so became his guardian as well as his beloved master. Lady Hurley remembers that her mother, Mrs. Crowther, regarded Blois as a frail little boy who needed building up with extra glasses of milk. From Brighton Grammar School he passed on to the University of Melbourne, and entered Trinity College as a student in medicine. Graduating with honours in 1913, he was appointed resident medical officer to the Royal Melbourne Hospital and later registrar. At first rejected on physical grounds for service in the Australian Imperial Force, he was subsequently accepted as a medical officer of the 3rd Australian General Hospital and saw service in Lemnos, Egypt, England and France. He was promoted to the rank of lieutenant-colonel and put in charge of the Medical Division till he was given his discharge in England in May, 1919. He had been mentioned in dispatches and created an Officer of the Most Excellent Order of the British Empire.

By examination, Blois Lawton became a member of the Royal College of Physicians in October, 1919, and later in 1932 was elected an Honorary Fellow. On his return to Melbourne he was appointed honorary physician to out-patients at the Royal Melbourne Hospital, and later in 1927 became honorary physician to in-patients, which position he held for 27 years. Retiring from the hospital in 1943, he was elected a consultant physician to the Royal Melbourne Hospital. The University of Melbourne had appointed him to be clinical tutor to students and also examiner in medicine in the final-year examinations of the medical course. He was a foundation member of The Royal Australasian College of Physicians, and for ten years was a member of the Board of Censors. At Trinity College he had been medical tutor from 1920 to 1922, and was made a member of the College Council in 1927, which position he held for 38 years. He practised as a consulting physician from 1920 to 1956, when he retired from active practice. During World War II he was consulting physician to the 115th Repatriation General Hospital, Heidelberg. For many years he was a member of the Medical Assessment Appeals Tribunal, and remained so up till the time of his death. He was appointed a Life Governor of the Royal Melbourne Hospital in 1944.

My first acquaintance with Blois Lawton was when he was in the Australian Imperial Force and we were both interested in *Schistosoma mansoni* infestation amongst the soldiers during the time in Egypt. He put on record the early symptoms of the disease in an article in this Journal of September 22, 1917. We had a most happy association and over the years had matters in common, and in the last few years we had sat together as the medical members on the War Pensions Assessment Appeal Tribunal in Melbourne.

Blois Lawton had not been robust, but he had conquered his infirmities. A warning of serious coronary damage had been given him 17 years prior to his death in July, 1961, and for the last six months he had carried on manfully and courageously. The final illness lasted only two days and he died, aged 74 years, in the Royal Melbourne Hospital, the institution with which he had been associated for 55 years, all his medical career, as student, resident medical officer, honorary physician and consultant physician. During his war service he met and married in London Sister Adele Baker, of Sydney, who had seen active service in Salonika. He leaves two married daughters and four grandchildren. His widow was not of a medical family like Blois, but her four brothers are lawyers practising in Sydney. Blois Lawton's career was a triumph, for with frail health, and doubly orphaned before the age of 11 years, he conquered these disabilities and rose to the front rank of consultant physicians.

Royal Australasian College of Surgeons.

PRIMARY EXAMINATION FOR FELLOWSHIP.

At the primary examination for fellowship of the Royal Australasian College of Surgeons, held in Melbourne, Sydney and Dunedin in September, 1961, the following candidates were approved: Barrie John Aarons, Wilton Campbell Carter, William Bruce Conolly, Graham Arthur Edwin Coupland, Donald Roy Kemp, John Miles Little, William Henry McCarthy, Donald Campbell McKinnon, Andrew Michael Munster, Nicholas Anthony Packham, Stuart Buckle Renwick, Vivian Frances Sorrell, Seon Choon Wong, David Ephraim Yoffa, Chee Keung Yu.

FACULTY OF ANÆSTHETISTS.

Primary Examination for Fellowship.

At the primary examination for fellowship of the Faculty of Anæsthetists of the Royal Australasian College of Surgeons, held in Melbourne, Sydney and Dunedin in September, 1961, the following candidates were approved: Francis Robert Berry, Hugh Cameron Butel, Geoffrey James Dalgarno, Brian William Daniels, Ian de Jersey, Charles McKinnon Holmes, John Francis Mainland, Arthur Frederic Woods.

University Intelligence.

THE UNIVERSITY OF SYDNEY.

Medical Research Fellowships.

Applications are invited for the following medical research fellowships of the University of Sydney for the year 1962: Reginald Maney Lake Scholarship and Amy Laura Bonamy Scholarship for pathological research; Anderson Stuart Memorial Research Fellowship, Marion Clare Reddall Scholarship and Joseph Goodburn-Smith Scholarship for research in any branch of medical science; Liston Wilson Fellowship for research in spastic paralysis or some closely allied subject; Norman Haire Fellowship for research in sexology, continuing and expanding work the nature of which is already being done in the Faculty of Medicine; Phyllis Anderson Research Fellowship for research in any branch of medical science; Sister Sanders Scholarship for part-time research work into some aspect of the diseases of children, with particular reference to the preventive aspect.

Fellowships are renewable for a second and, in certain circumstances, for a third year. All fall due on January 1, 1962. All are to the value of £1831 or £2231 *per annum* according to qualifications and experience except the Phyllis Anderson Research Fellowship, which is to the value of £1831 or £2500 *per annum*, and the Sister Sanders Scholarship, which is to the value of £500 *per annum*.

Applications for fellowships for 1962 should be made to the Registrar, and will close on Friday, November 24, 1961.

The fellowships for 1962 will be awarded in December, 1961. Applications forms may be obtained from the Registrar's office. Details of the fellowships are given in the "Calendar of the University of Sydney" for 1961, at pages 413 to 417.

Public Health.

DEPARTMENT OF PUBLIC HEALTH OF NEW SOUTH WALES.

Decentralization of Departmental Activities and Alteration of Boundaries of Health Districts.

THE following statement is published at the request of the Under-Secretary of the Department of Public Health of New South Wales.

In accordance with Government policy, the Department has prepared a plan for the decentralization of many departmental activities, through its medical officers of health. The areas of the present health districts are to be enlarged, and two additional health districts will be created in the near future. This will result in practically the whole of the State being incorporated within these districts. The new areas were gazetted on September 15, 1961.

The Board of Health has approved of the following variation of titles of some of the present health districts: Metropolitan Health District, unchanged. Hunter River Health District will become the Newcastle Health District. The South Coast Health District title is unchanged. The Richmond-Tweed Health District will become the North Coast Health District. The Mitchell Health District will become the Western Health District. Broken Hill Health District will also remain unchanged.

The boundaries of all present districts, except Broken Hill, will be altered, and in future each will consist of the municipalities and shires as listed hereunder:

Metropolitan Health District.

Municipalities.—City of Sydney, Ashfield, Auburn, Bankstown, Blacktown, Botany, Burwood, Camden, Campbelltown, Canterbury, Concord, Drummoyne, Fairfield, Holroyd, Hunter's Hill, Hurstville, Kogarah, Ku-ring-Gai, Lane Cove, Leichhardt, Liverpool, Manly, Marrickville, Mosman, North Sydney, City of Parramatta, City of Penrith, Randwick, Rockdale, Ryde, Strathfield, Waverley, Willoughby, Windsor, Woollahra, The Harbour of Port Jackson.

Shires.—Baulkham Hills, Hornsby, Sutherland, Warringah.

Newcastle Health District.

Municipalities.—City of Maitland, City of Newcastle, City of Greater Cessnock, Kempsey, The Harbour of Port Hunter, Muswellbrook, Port Macquarie, Singleton, Taree, Wingham.

Shires.—Dungog, Gloucester, Gosford, Hastings, Lake Macquarie, Macleay, Manning, Merriwa, Muswellbrook, Patrick Plains, Port Stephens, Scone, Stroud, Wyong.

South Coast Health District.

Municipalities.—Bega, Bowral, Bombala, Cooma, City of Goulburn, City of Greater Wollongong, Kiama, Queanbeyan, Shellharbour.

Shires.—Bibbenluke, Crookwell, Eurobodalla, Gunning, Imlay, Mittagong, Monaro, Mulwaree, Mumbulla, Shoalhaven, Snowy River, Tallanganda, Wingecarribee, Wollondilly, Yarrowlumla.

Western Health District.

Municipalities.—City of Bathurst, City of Blue Mountains, Condobolin, Cowra, Dubbo, Forbes, City of Lithgow, Mudgee, Narromine, Nyngan, City of Orange, Parkes, Peak Hill.

Shires.—Abercrombie, Blaxland, Bogan, Boree, Brewarrina, Canobolas, Cobar, Coli, Coolah, Coonabarabran, Coonamble, Cudgegong, Darling, Gilgandra, Goobang, Jemalong, Lachlan, Lyndhurst, Molong, Oberon, Rylstone, Talbragar, Timbrebongie, Turon, Walgett, Warren, Waugoola, Wellington.

North Coast Health District.

Municipalities.—Ballina, Casino, City of Grafton, City of Lismore, Mullumbimby.

Shires.—Bellingen, Byron, Coff's Harbour, Copmanhurst, Gundurimba, Kyogle, Maclean, Nambucca, Nymboida, Terania, Tintenbar, Tomki, Tweed, Ulmarra, Woodburn.

Responsibilities of Medical Officers of Health.

Eventually, the medical officers of health will be responsible within their districts for: (*a*) supervision of health of the community; (*b*) health education; (*c*) supervision of the health activities of local authorities, including environmental sanitation and pure food inspection; (*d*) departmental administration relating to: (i) maternal and baby welfare, (ii) school medical service, (iii) private hospitals, (iv) dental services, (v) tuberculosis control.

The proposed two additional health districts will be the North Western Health District with Headquarters at Tamworth, and the Riverina Health District with headquarters at Cootamundra.

The College of Radiologists of Australasia.

RESULTS OF EXAMINATIONS FOR MEMBERSHIP.

THE names of the successful candidates in Part II of the examinations for membership of the College of Radiologists of Australasia, held in August, 1961, are as follows:

In radiodiagnosis: Dr. A. Bardsley, Dr. M. S. Benson, Dr. Fay Grote, Dr. S. Manea and Dr. A. D. Smythe, Victoria; Dr. G. J. Harrington and Dr. T. S. Lamond, New South Wales.

Naval, Military and Air Force.

APPOINTMENTS.

THE following appointments, changes, etc., are published in the *Commonwealth of Australia Gazette*, No. 70, of September 7, 1961.

NAVAL FORCES OF THE COMMONWEALTH.

Citizen Naval Forces of the Commonwealth.

Royal Australian Naval Reserve.

Appointment.—Francis Bursill Fowler is appointed Surgeon Lieutenant, dated 4th October, 1960.

Promotions.—Surgeon Lieutenant Arthur Henry Keech is promoted to the rank of Surgeon Lieutenant-Commander, dated 17th June, 1961.

Resignation.—The resignation of Albert Pfeifer of his appointment as Surgeon Lieutenant is accepted, dated 24th May, 1961.

ROYAL AUSTRALIAN AIR FORCE.

Permanent Air Force.

Medical Branch.

The probationary appointment of each of the following Flight Lieutenants is confirmed:—S. Murphy (0310788), R. D. B. Leicester (0310791).

The resignation of Flight Lieutenant R. P. Quirk (0314324) is accepted, 9th June, 1961.

Active Citizen Air Force.

Medical Branch.

No. 22 (City of Sydney) (Auxiliary) Squadron.—Flight Lieutenant D. C. Mackenzie (0211189) is transferred to the Reserve, 8th June, 1961.

Notes and News.

Australian Radiation Society (N.S.W. Branch).

We have been asked to draw attention to the recently formed New South Wales Branch of the Australian Radiation Society. (It is hoped that amalgamation with the Victorian Branch will be finalized shortly.) The aim of the Society is to bring the various radiation workers together at meetings and conferences, so that a better understanding of ideas from the different fields of endeavour can be effected. Its objects are stated in its constitution to be as follows:

(*a*) To encourage radiation research in New South Wales.

(*b*) To provide a forum for the exchange of radiation information between members and for criticism of work, by discussion on subjects of interest to members and by the presentation of papers.

(c) To arrange lectures and visits by persons with special knowledge in this field.

The number of participants in the radiation research field in Australia is quite small, and they are widely scattered throughout many different professions such as physics, chemistry, biology and medicine. However, it is thought that there must be many people interested in radiation research who are as yet unaware of the existence of the Radiation Society, and it is hoped to enlarge the active membership of the society substantially if more people can be made aware of it.

Ordinary membership is open to all persons who are interested in radiobiology; subscription rates for new members are £1 for the first year (10s. in the case of students) and 10s. *per annum* thereafter. The address of the honorary secretary is: I. S. Jenkinson, Physics Department, St. Vincent's Hospital, Sydney.

Open Day at Lucas Heights.

The Australian Atomic Energy Commission Research Establishment, Lucas Heights, will hold an open day on Friday, December 8, 1961, from 9.30 a.m. to 4.30 p.m. This open day has been arranged to enable members of professional associations and societies to inspect the work at the Research Establishment, which embraces many fields of science and engineering. Tickets for the open day will be available from the secretaries of professional associations and societies, or on application to the Director, Australian Atomic Energy Commission, Private Mail Bag, Sutherland, N.S.W.

Royal Australian Army Medical Corps, Eastern Command: Annual Dinner.

The officers of the Royal Australian Army Medical Corps, Eastern Command, will hold their third annual Corps Day dinner on Saturday, November 18, 1961, at the Imperial Service Club, Barrack Street, Sydney. The Director-General of Medical Services, Major-General A. J. Clyne, C.B.E., and the Honorary Colonel, Brigadier J. Steigrad, C.B.E., E.D., will be present. Officers of the Active Reserve and Retired Lists are invited to attend, and it is hoped that many officers who served in the Corps during wartime will do so. Prior to dinner, a wreath will be laid at the Cenotaph, where those attending are requested to assemble at 6 p.m. Dress is No. 9 or No. 2 uniform, or dinner jacket, with which miniature medals may be worn. The cost is £3 inclusive. For reservations or inquiries, those interested are asked to telephone Major E. Pretty, Eastern Command Depot of Medical Stores, 34-1735, or Lieutenant-Colonel R. D. Rothfield, 31-0411, Extension 255.

Summer Camps for Diabetic Children.

The Association of Summer Camps for Diabetic Children announces that the annual camp will be held from January 13 to 27, 1962, at the Fairbridge Farm School, Molong, N.S.W. Any diabetic boy or girl between the ages of six and 11 years is eligible to attend. Applications close on November 30, 1961. The camp will be under the supervision of a qualified medical staff. Information may be obtained from the Honorary Secretary, Miss R. Pirie, c.o. Dietitian's Office, Royal North Shore Hospital of Sydney, St. Leonards.

Appointment of Commonwealth Serum Laboratories Commissioners.

The Minister for Health, Dr. D. A. Cameron, has announced the names of the Commissioners who will administer the Commonwealth Serum Laboratories, Melbourne. The Laboratories were formerly under the control of the Department of Health. The four part-time Commissioners will be: (i) Chairman, Mr. C. S. Butt, who has been appointed for two years. Mr. Butt was formerly chairman, and is now a director of Olympic Consolidated Industries Ltd., and associated companies. He was honorary Commonwealth Controller of Rubber from 1942 to 1945. (ii) Vice-Chairman, Mr. J. A. Hancock, appointed for four years. Mr. Hancock, who is a chartered accountant, is a partner in the firm of Hancock and Woodward. He is a director of a number of companies. (iii) Professor E. S. J. King, appointed for four years. Professor King is Professor of Pathology at the University of Melbourne, and is a member of the National Health and Medical Research Council. (iv) Mr. O. G. Meyer, O.B.E., E.D., appointed for two years. Mr. Meyer, who is managing director of Australian Carbon Black

DISEASES NOTIFIED IN EACH STATE AND TERRITORY OF AUSTRALIA FOR THE WEEK ENDED SEPTEMBER 23, 1961.[1]

Disease.	New South Wales.	Victoria.	Queensland.	South Australia.	Western Australia.	Tasmania.	Northern Territory.	Australian Capital Territory.	Australia.
Acute Rheumatism	1	..	..	1	..	..	..	..	2
Amœbiasis	..	..	..	..	..	..	..	..	..
Ancylostomiasis	1	..	1	..	..	..	..	..	2
Anthrax	..	..	..	..	..	..	..	..	..
Bilharziasis	..	..	..	..	..	..	..	..	..
Brucellosis	..	..	..	..	1	..	..	..	1
Cholera	..	..	..	..	..	..	..	..	..
Chorea (St. Vitus)	..	..	..	..	..	..	..	..	..
Dengue	..	..	..	..	..	..	..	..	..
Diarrhœa (Infantile)	8(7)	1(1)	..	..	2	5	..	..	16
Diphtheria	..	..	..	..	1(1)	..	..	..	1
Dysentery (Bacillary)	..	..	..	8(4)	5	..	..	..	13
Encephalitis	..	..	..	..	..	..	..	..	..
Filariasis	..	..	..	..	..	..	..	..	..
Homologous Serum Jaundice	..	..	..	1	..	..	..	..	1
Hydatid	..	..	..	..	..	..	..	..	..
Infective Hepatitis	109(39)	48(27)	16(7)	29(12)	1(1)	8(6)	..	9	220
Lead Poisoning	..	..	2	..	..	..	..	..	2
Leprosy	..	..	..	..	3	..	7	..	10
Leptospirosis	..	..	6	..	..	..	..	..	6
Malaria	..	..	..	..	..	..	..	..	..
Meningococcal Infection	1	2	..	..	..	..	..	..	3
Ophthalmia	..	..	..	..	..	..	..	..	..
Ornithosis	..	..	..	..	..	..	..	..	..
Paratyphoid	..	..	..	..	..	..	..	..	..
Plague	..	..	..	..	..	..	..	..	..
Poliomyelitis	4	..	..	1(1)	..	..	..	..	5
Puerperal Fever	..	..	1	..	..	..	..	..	1
Rubella	..	16(13)	2(2)	3(1)	4(3)	1	..	..	26
Salmonella Infection	..	..	..	..	..	..	..	..	..
Scarlet Fever	4(3)	5(4)	4(3)	3(1)	3(3)	..	..	..	19
Smallpox	..	..	..	..	..	..	..	..	..
Tetanus	..	1(1)	..	..	..	..	..	..	1
Trachoma	..	..	..	..	3	..	..	..	3
Trichinosis	..	..	..	..	..	..	..	..	..
Tuberculosis	25(12)	16(9)	16(3)	3(3)	9(8)	4(2)	..	..	73
Typhoid Fever	..	..	..	..	..	..	..	..	..
Typhus (Flea-, Mite- and Tick-borne)	..	..	..	..	..	..	..	..	..
Typhus (Louse-borne)	..	..	..	..	..	..	..	..	..
Yellow Fever	..	..	..	..	..	..	..	..	..

[1] Figures in parentheses are those for the metropolitan area.

Pty. Ltd., Victoria, was a Victorian Railways Commissioner from 1950 to 1958. All four Commissioners live in Melbourne. The new Director of the Commonwealth Serum Laboratories, who will be the only full-time member of the Commission, will be Dr. R. W. Greville, a former senior medical officer in the Consultant Division of the Commonwealth Serum Laboratories, who is at present Medical Superintendent at Geelong and District Hospital, Victoria. Dr. Greville was a captain in the Royal Australian Army Medical Corps from 1940 to 1945. The Commission will assume control of the Laboratories from November 2, 1961.

Eye, Ear and Throat Hospital.

The first International Symposium of the Manhattan Eye, Ear and Throat Hospital, New York City, will be held on May 21 to 25, 1962. The subject of the symposium is "Plastic and Reconstructive Surgery of the Eye, Eyelids and Adnexa". The Honorary President is Professor V. H. Kazanjian, the Chairman is Professor R. C. Troutman, and the Programme Chairmen are Professor J. H. Converse and Dr. Byron Smith. The Executive Committee is as follows: Professor J. Barraquer, Professor B. F. Boyd, Dr. Blair O. Rogers, Sir Benjamin Rycroft and Professor K. Schuchardt. The registration is $100 for the United States and Canada, and $50 for other countries. Further information may be obtained by writing to the Chairman, Professor Richard C. Troutman, at the Manhattan Eye, Ear and Throat Hospital, 210 East 64th Street, New York 21, N.Y.

British Medical Association.

VICTORIAN BRANCH.

Section of Preventive Medicine.

THE annual meeting of the Section of Preventive Medicine of the Victorian Branch of the British Medical Association will be held in the Medical Society Hall, 426 Albert Street, East Melbourne, at 4.20 p.m., on Thursday, November 9, 1961. After the meeting Dr. W. J. Stevenson will give an address on "Public Health Trends Overseas". All those interested are invited to attend this address.

Post-Graduate Work.

SURGICAL SEMINARS AT ST. VINCENT'S HOSPITAL, SYDNEY.

A SURGICAL SEMINAR will be held at St. Vincent's Hospital, Sydney, on Monday, November 6, 1961, at 5.30 p.m., in the fifth floor lecture theatre. Mr. C. F. Thwaites will discuss "Some Aspects of Lumbar Sympathectomy". All medical practitioners are invited to attend.

Nominations and Elections.

THE undermentioned has applied for election as a member of the New South Wales Branch of the British Medical Association:

Endre, Andrew Joseph Zoltan, M.D., 1934 (Univ. Budapest). Reg. under Section 17 (2B), *Medical Practitioners Act*, 1938 (as amended), 290 Canley Vale Road, Canley Heights.

Deaths.

THE following death has been announced:

ALLEN.—Cecil Gordon Allen, on October 11, 1961, at Sydney, New South Wales.

Diary for the Month.

OCTOBER 21.—Victorian Branch, B.M.A.: Country Branch Meeting (Bendigo).
OCTOBER 24.—New South Wales Branch, B.M.A.: Hospitals Committee.
OCTOBER 25.—Victorian Branch, B.M.A.: Branch Council.
OCTOBER 26.—South Australian Branch, B.M.A.: Scientific Meeting.
OCTOBER 27.—Queensland Branch, B.M.A.: Council Meeting.
OCTOBER 28.—New South Wales Branch, B.M.A.: Branch Meeting.

Medical Appointments: Important Notice.

MEDICAL PRACTITIONERS are requested not to apply for any appointment mentioned below without having first communicated with the Honorary Secretary of the Branch concerned, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

New South Wales Branch (Medical Secretary, 135 Macquarie Street, Sydney): Medical Officers to Sydney City Council. All contract practice appointments in New South Wales. Members are requested to consult the Medical Secretary before undertaking practice in dwellings owned by the Housing Commission.

South Australian Branch (Honorary Secretary, 80 Brougham Place, North Adelaide): All contract practice appointments in South Australia.

Editorial Notices.

ALL articles submitted for publication in this Journal should be typed with double or treble spacing. Carbon copies should not be sent. Authors are requested to avoid the use of abbreviations, other than those normally used by the Journal, and not to underline either words or phrases.

Authors of papers are asked to state for inclusion in the title their principal qualifications as well as their relevant appointment and/or the unit, hospital or department from which the paper comes.

References to articles and books should be carefully checked. In a reference to an article in a journal the following information should be given: surname of author, initials of author, year, full title of article, name of journal, volume, number of first page of article. In a reference to a book the following information should be given: surname of author, initials of author, year of publication, full title of book, publisher, place of publication, page number (where relevant). The abbreviations used for the titles of journals are those of the list known as "World Medical Periodicals" (published by the World Medical Association). If a reference is made to an abstract of a paper, the name of the original journal, together with that of the journal in which the abstract has appeared, should be given with full data in each instance.

Authors submitting illustrations are asked, if possible, to provide the originals (not photographic copies) of line drawings, graphs and diagrams, and prints from the original negatives of photomicrographs. Authors who are not accustomed to preparing drawings or photographic prints for reproduction are invited to seek the advice of the Editor.

Original articles forwarded for publication are understood to be offered to THE MEDICAL JOURNAL OF AUSTRALIA alone, unless the contrary is stated.

All communications should be addressed to the Editor, THE MEDICAL JOURNAL OF AUSTRALIA, The Printing House, Seamer Street, Glebe, New South Wales. (Telephones: 68-2651-2-3.)

Members and subscribers are requested to notify the Manager, THE MEDICAL JOURNAL OF AUSTRALIA, Seamer Street, Glebe, New South Wales, without delay, of any irregularity in the delivery of this Journal. The management cannot accept any responsibility or recognize any claim arising out of non-receipt of journals unless such notification is received within one month.

SUBSCRIPTION RATES.—Medical students and others not receiving THE MEDICAL JOURNAL OF AUSTRALIA in virtue of membership of the Branches of the British Medical Association in Australia can become subscribers to the Journal by applying to the Manager or through the usual agents and booksellers. Subscriptions can commence at the beginning of any quarter and are renewable on December 31. The rate is £6 *per annum* within Australia and the British Commonwealth of Nations, and £7 10s. *per annum* within America and foreign countries, payable in advance.